From the Department of Women's and Children's Health
Karolinska Institutet, Stockholm, Sweden

PRETERM BIRTH -

Parents' experiences, affect, stress and inflammatory markers

Emma Fransson

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ABSTRACT

Preterm birth (PTB), before 37 completed weeks of gestation, is the principal risk factor for neonatal morbidity and mortality. In Sweden about 5.6% of pregnant women deliver preterm. The etiology of PTB is not fully understood, but it has been suggested that the underlying mechanisms could have both biological and psychosocial origins. Parents' health and experiences in association with PTB have been quite overlooked, particularly those of the fathers and of parents of infants born late preterm. However, stress in parents has been suggested to influence the parent's caregiving capacity. The aim of this thesis was to gain further understanding of the psychosocial contribution to the etiology of PTB, of a possible inflammatory pathway for the psychosocial contribution and of the consequences of PTB for parents' health and experiences of caregiving.

Study I is a population-based study where the association between antenatal scores of depressive symptoms and PTB was investigated. The results show that depressive symptoms contribute to increased risk for PTB, also after adjusting for other known risk factors for PTB.

In Study II it was investigated if affectivity differs between mothers with PTB and mothers with term birth and if maternal and umbilical cord serum cytokines differ between these groups. Further, if there are associations between mothers' emotions and maternal and cord cytokines at preterm and term birth. The findings indicate associations between negative emotions and both maternal and neonate immune activity in PTB.

Study III is an interview study of first-time parents' experiences of early and late PTB. The findings show hindering and facilitating factors in the development of parents' caregiving. Difficulties for mothers and fathers in both groups were attributed both to physical hinders, such as separation from the infant and to emotional hinders, such as fear, worry or few cues from the infant. Hinders were also attributed to the clinical practices. Facilitating factors were mental or physical closeness to the infant, being together as parents as well as support from the staff.

Study IV aimed at investigating levels of and associations between perceived stress and an inflammatory marker, comparing parents of preterm and full term infants at two time-points. Mothers of infants born preterm showed higher stress levels early post partum, compared to the term group. The stress declined over time and was comparable to levels in the term group at infant age four months. Subgroup analyses showed greater stress in mothers of infants born early preterm at both time-points compared to the term group. In fathers, no differences in stress levels were found between the preterm and term groups but fathers of infants born early preterm reported higher stress levels early post partum than fathers of infants born late preterm. No associations were found between stress levels and the inflammatory marker. In parents of preterm infants, high levels of stress at infant age four months were predicted by stress levels early post partum.

The results support the notion of psychosocial contribution to the etiology of PTB via an inflammatory pathway. Future studies in this area should preferably include both psychological and biological markers. The findings also reveal hindering and facilitating factors to parents' early caregiving after PTB and elevated stress levels, particularly in parents of infants born early preterm, suggesting a further need to support these parents.

LIST OF PUBLICATIONS

I Fransson E, Örtenstrand A and Hjelmstedt A. (2011). Antenatal depressive symptoms and preterm birth: a prospective study of a Swedish national sample. *Birth,* 38:10-6

II Fransson E, Dubicke A, Byström B, Ekman-Ordeberg G, Hjelmstedt A[*] and Lekander M[*]. (2011). Negative emotions and cytokines in maternal and cord serum at preterm birth. *American Journal of Reproductive Immunology.* Online publication 21 Oct.

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IV Fransson E, Böhm B, Mothander PR, Ekman-Ordeberg G, Byström B, Lekander M and Hjelmstedt A. Stress and IL-6 in parents of preterm infants in comparison to parents of term infants. *Submitted manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
ANS	Autonomic nervous system
ART	Assisted reproductive technology
ASQ:SE	Ages and Stages Questionnaire: Social Emotional
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CPAP	Continuous positive airway pressure
ELISA	Enzyme-linked immune sorbent assay
EPDS	Edinburgh Postnatal Depression Scale
FIRS	The Fetal inflammatory response syndrome
HPA	Hypothalamic-pituitary-adrenal (axis)
IFN	Interferon
IL	Interleukin
LOD	Limit of detection
NA	Negative affect
NICU	Neonatal Intensive Care Unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Program
PA	Positive affect
PANAS	The Positive and Negative Affect Schedule
PSS	The Perceived Stress Scale
PPROM	Preterm prelabor rupture of fetal membranes
PTB	Preterm birth
PVL	Periventricular leucomalacia
ROP	Retinopathy of prematurity
SD	Standard deviation
SMBR	Swedish medical birth registry
TB	Term birth
TGF	Transforming growth factor
Th	T helper (cells)
TNF	Tumor necrosis factor
Treg	Regulatory T (cells)
WHO	World Health Organization

SAMMANFATTNING [IN SWEDISH]

Prematur förlossning (före 37 fullgångna veckor), är ett världsomspännande problem och den största enskilda riskfaktorn för neonatal dödlighet och sjuklighet. Andelen barn som föds prematurt varierar världen över, från 5.6% i Sverige, cirka 12% i USA upp till 17% i delar av Afrika. Trots ökad kunskap om hur vi bäst räddar och vårdar för tidigt födda barn, så har forskningen hittills inte kunnat bidra till en minskning av andelen prematura förlossningar. Prematur förlossning kan delas in i spontan prematur förlossning och prematur förlossning på medicinsk indikation (t ex att kvinnan har havandeskapsförgiftning). Man vet idag inte exakt vad som orsakar spontan prematur förlossning, men såväl biologiska som psykosociala riskfaktorer har identifierats. Psykosociala faktorer såsom stress och nedstämdhet har ansetts kunna påverka immunförsvaret, vilket i sin tur kan påverka graviditeten.

Det finns inte så mycket tidigare forskning kring pappors upplevelser och hälsa i samband med prematur förlossning. Studier saknas också av föräldrar till barn som föds lite (fem-sex veckor) för tidigt. Syftet med studierna i denna avhandling har varit att öka kunskapen om huruvida psykosociala faktorer ökar risken för prematur förlossning och om psykosociala faktorer påverkar inflammatoriska processer i samband förlossning. Dessutom undersöktes föräldrars upplevelser i samband med prematur förlossning och föräldrars stress och markörer för inflammation (cytokiner) tidigt efter barnets födelse samt då barnet var fyra månader (korrigerad ålder för barn födda prematurt).

Studie I bygger på en nationell svensk enkätundersökning med drygt 2900 kvinnor. Här undersöktes om depressiva symtom, mätt vid ett tillfälle i tidig graviditet, ökar risken för prematur förlossning. Resultatet visar på en viss riskökning för prematur förlossning, även när man kontrollerar för andra kända riskfaktorer (såsom sociala faktorer, mammans ålder och rökning).

Studie II-IV baseras på en studiegrupp om 80 familjer varav 40 med spontan prematur förlossning och 40 med förlossning i fullgången graviditet.

I Studie II studerades samband mellan å ena sidan depressiva symtom och positiv/negativ affekt hos mamman och å andra sidan markörer för inflammation (cytokiner) i hennes blod respektive i navelsträngsblod vid prematur förlossning och förlossning i fullgången tid. Denna studie visar ett samband mellan depressiva symtom/negativ affekt och förhöjda nivåer av inflammatoriska cytokiner i blodprov från mammor vid förlossning och i navelsträngs-prover. Detta samband ses endast i prematurgruppen.

Studie III är en intervjustudie kring förstagångsföräldrars upplevelser av att bli föräldrar till barn födda mycket (upp till tre månader) respektive lite (fem-sex veckor) för tidigt. Resultaten visar på försvårande och underlättande faktorer för föräldrars omvårdnad av barnet. Föräldrar till barn födda mycket prematurt upplever att omvårdnaden av barnet försvåras av separation från barnet, osäker prognos samt upplevda rollkonflikter hos en del pappor. Underlättande faktorer är tilltro till barnets överlevnadskapacitet, förmågan att anpassa sina förväntningar och att känna sig betydelsefull som förälder. Hinder för föräldrars omvårdnad av barn födda några veckor för tidigt kan vara förälderns osäkerhet kring barnets

hälsotillstånd och svårigheter att få kontakt med barnet och eller att tolka barnets signaler. Underlättande faktorer kan vara att man känner sig förberedd på föräldraskapet och att man får familjerum på BB.

I studie IV undersöktes upplevd stress och inflammatoriska cytokiner vid två tillfällen hos föräldrar vars barn fötts för tidigt jämfört med föräldrar till barn födda i fullgången tid, dels på BB samt då barnet var 4 månader (korrigerad ålder för prematuritet). Mammor till barn födda för tidigt rapporterade högre stress på BB jämfört med mammor till barn födda i fullgången tid. Då barnen var fyra månader var stressnivåerna jämförbara mellan grupperna. Pappornas stressnivåer skilde sig inte åt mellan grupperna. Vid en jämförelse av undergrupper rapporterade pappor till barn födda mycket för tidigt högre stress initialt jämfört med pappor vars barn fötts lite för tidigt. Mammor till barn födda mycket prematurt hade hög stressnivå vid båda tillfällena. För föräldrar till barn födda prematurt kan hög stress under BB tiden predicera hög stress då barnet är fyra månader, vilket kan innebära att man tidigt skulle kunna identifiera föräldrar i behov av extra stöd.

Resultaten i avhandlingen pekar på att psykosociala faktorer kan öka risken för prematur förlossning och att detta skulle kunna ske via inflammatoriska processer. Resultaten visar också på hinder och underlättande faktorer i föräldrars tidiga omhändertagande av barn födda prematurt samt förhöjd stress hos föräldrar efter prematur förlossning, i synnerhet bland föräldrar till mycket för tidigt födda barn. Resultaten indikerar att föräldrar med risk för förhöjd stress under de första månaderna kan identifieras redan på BB, vilket skulle kunna underlätta stödinsatser till dessa föräldrar. Vården av familjer med barn födda prematurt kan också underlättas om föräldrarna kan vara tillsammans på BB samt om vården bereder möjlighet för nära kontakt mellan föräldrar och barn.

BACKGROUND

Introduction

Preterm birth (PTB) is the principal risk factor for neonatal morbidity and mortality (Saigal & Doyle 2008). The etiology of spontaneous PTB is not fully understood, but it has been suggested that the mechanisms could have both biological and psychosocial origins (Goldenberg et al 2008). Stress and depressive symptoms have been shown to modulate inflammatory activity in pregnant women (Christian et al 2009; Coussons-Read et al 2007). Accordingly, it has been suggested that psychosocial factors might contribute to PTB via inflammatory processes.

Parents' health and experiences in association with PTB have been quite overlooked, particularly that of fathers and of parents of infants born late preterm. However, stress in parents could influence the quality of parental functioning and caregiving capacity (Davis et al 2003a; Muller-Nix et al 2004; Treyvaud et al 2010; Zelkowitz et al 2009).

In this thesis, PTB will be studied from different perspectives to gain further understanding of the psychosocial contribution to PTB, of possible pathways for such psychosocial contribution via inflammatory processes, as well as of the consequences of PTB for parents' health and experiences of caregiving, see figure 1.

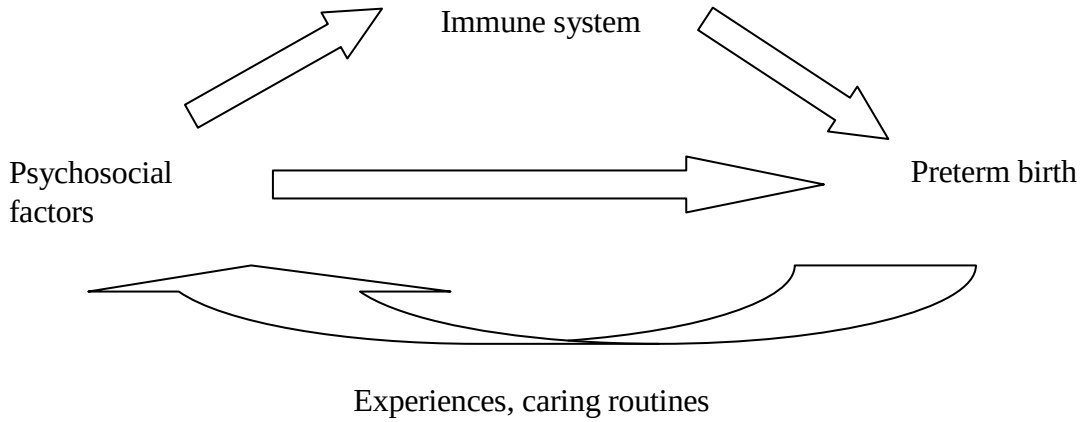

Figure 1. Possible associations investigated in this thesis.

Preterm birth

Preterm birth (PTB) is defined by the World Health Organization (WHO) as birth occurring before 37 completed weeks of pregnancy. WHO-data from 2005 show that 12.9 million births or 9.6% of all births worldwide occur preterm (Beck et al 2010). However, the PTB rate varies significantly across the world. The highest rates, 14-17%, are found in southern and eastern Africa, in North America the rates are 10-13%, in South America 8%, in Asia the rates vary between 4-9% and in Europe around 6% of births occur preterm. The PTB rate in Sweden was 5.6% in 2008 and about 1.2% of the deliveries occurred before 33 completed weeks of pregnancy (Swedish Board of Health and Welfare, 2011).

Globally, PTB is the most important single cause of neonatal death (Black et al 2010). PTB is also associated with great costs for the healthcare systems (Beck et al 2010). There has been increased focus on long term follow-up of preterm infants, and the conclusion is that PTB is a major contributor to recurrent health problems both in infants and children (Saigal & Doyle 2008). However, in many parts of the world, neonatal intensive care has improved considerably during the past decades which has resulted in higher survival rates, especially of infants born extremely preterm (Wilson-Costello et al 2005).

Infants and children born preterm

Very preterm birth, before 28 completed weeks of gestation, is associated with a substantial increase in the risk of neonatal mortality, as well as of neurodevelopmental impairments (Saigal & Doyle 2008). However, also infants born late preterm, in gestational week 34-36, are at higher risk of neonatal mortality (Kramer et al 2000; Shapiro-Mendoza et al 2008) as well as of temperature instability, hypoglycemia, respiratory distress, infection, jaundice and feeding difficulties (Engle et al 2007; Saigal & Doyle 2008). Additionally, children born both early and late preterm are reported to be at increased risk of long term mortality (Crump et al 2011) and of long term health problems (Saigal & Doyle 2008; Yu & Dong 2011).

The long term complications connected with prematurity originate mainly from problems in three domains: the brain, the respiratory system and the visual system, together with an increased overall risk of infection. The brain of a preterm infant born at 24 weeks of gestation has not yet gone through the folding of the cortex. Moreover, maternal and neonatal infections as well as asphyxia and hypoxia/ischemia are associated with damage in the white

matter around the lateral cerebral ventricles (periventricular leucomalacia; PVL). The severe grades of PVL interfere with normal cortical organization and are associated with cerebral palsy. In addition, the preterm brain is especially vulnerable to insults due to unstable vascularization and fragile vessels and, in addition, the blood pressure is often irregular. This increases the risk of bleeding inside or around the ventricles, which in severe stages is also associated with cerebral palsy as well as with developmental psycho-motor problems. Swedish studies have shown a moderate impact of PTB on neurological dysfunctions in children born preterm, e.g. cognitive performance and school-related problems (Böhm et al 2010; Böhm et al 2004; Ekéus et al 2010; Hallin et al 2010; Lindström et al 2011).

The lungs are not developed for unassisted breathing until about the 28th week of pregnancy. Accordingly, breathing is often irregular and apneas are frequent, even in infants born late preterm. To promote fetal lung development, women with threatening PTB are given corticosteroid treatment before birth. In Sweden, such treatment is usually given in pregnancies before 34 completed weeks. The respirator-incubator and equipment to produce continuous positive airway pressure (CPAP) have signified great progress in the survival of preterm infants. However, some infants need ventilation support for a long time and chronic lung disease is a common complication after PTB (Broström et al 2010; Vogt et al 2011).

Retinopathy of prematurity (ROP) is a complication of the immature visual system in combination with oxygen supplementation. Recent advances in treatment of ROP have improved the outcomes, but ROP is still a major cause of visual loss in children born preterm (Salvin et al 2010). In addition, visual impairment after PTB could also be attributed to cerebral visual impairment associated with PVL as the damaged brain region in the severe stages of PVL is situated close to the lateral visual tract (Jacobson & Dutton 2000).

Furthermore the social and emotional development of the child might be affected by PTB. Studies on attachment in infants and toddlers born preterm have shown lower proportions of secure attachment, especially in infants born very preterm and/or infants who were very ill during their first period of life (Mangelsdorf et al 1996; Plunkett et al 1986; Udry-Jorgensen et al 2011). In addition, adolescents who were born extremely preterm more often show insecure classifications of attachment (Hallin et al 2011) and report less social interaction compared to peers born at term (Hallin & Stjernqvist 2011). However, there are also findings indicating that maternal representations, (i.e. the mothers memories and experiences of attachment and caregiving, see for example Stern-Bruschweiler & Stern, 1989), contribute

more to infants' secure attachment than do infant disabilities (Cox et al 2000; van Ijzendoorn et al 1992). A recent review concludes that prematurity per se does not increase the risk of developing poor attachment quality (Korja et al 2011).

Transition to parenthood

The developmental process that takes place when a person proceeds from being a man or a woman to also becoming a parent has been described as the transition to parenthood (Draper 2003; Habib & Lancaster 2006; LaRossa & Sinha 2006). This transition has also been illustrated as the emergence of a new mental organization (Stern 1998). Stern has described this as a temporary but potentially long term change, with new life goals including ensuring the infant's survival and letting the infant become the primary focus. The psychological preparation for parenthood may start long before the actual pregnancy, but is enhanced during pregnancy (Genesoni & Tallandini 2009; Stern & Bruschweiler-Stern 1998). The parents-to-be could experience preoccupation with fantasies about the infant as well as increased sensitivity, which is suggested to act as preparation for parenthood (Stern & Bruschweiler-Stern 1998). Moreover, antenatal engagement in the offspring is suggested to predict engagement post partum (Figueiredo & Costa 2009). However, when the infant is born preterm the psychological preparation for parenthood is interrupted (Zeanah & McDonough 1989) and the development of the new role and the relationship with the infant can be hindered by fear and worry about the infant's health or survival (Lindberg & Öhrling 2008; Sloan et al 2008). If the infant is born early preterm, the perception of the infant could be quite different from what the parents expect. Furthermore, PTB is associated with prolonged hospital stay, sometimes in an intensive care environment, that could be intimidating for parents (Gavey 2007; Reid 2000).

Parents' caregiving

An important aspect of the transition to parenthood is the development of the parental caregiving system. This system has been described as complementary to the child's attachment system. The concept of attachment was introduced by John Bowlby as a genetically programmed behavioral system, with the evolutionary goal of the child's survival. The attachment bond is thought to sustain the child's close proximity to the caregiver to enable protection from possible dangers (Bowlby 1969/1982). The attachment system becomes activated when the child perceives a situation as threatening or stressful.

Bowlby described the parents' caregiving as a corresponding behavioral system, sharing the same goals of care and protection as the attachment system. Caregiving has also been suggested as a mature transformation of attachment (Solomon & George 1996), derived from mental representations of caregiving (George & Solomon 1989). The description of the caregiving system has been criticized for not acknowledging the emotions involved in caregiving and for not thoroughly explaining why elements such as sensitivity are important for the parents (Bell & Richard 2000). Others have argued that while proximity-seeking in caregiving is observed across species (Dozier 2000) the emotional elements, such as warmth or sensitivity, are not necessary constituents in caregiving (Geary 2000).

Caregiving has also been described as involving both biological and experiential factors (George & Solomon 2008). Thus, childhood experience, the social context of caregiving, as well as hormones and brain activation in parent-infant contact could influence caregiving quality (Storey et al 2000; Swain et al 2007). Parallel to the attachment system, the parent's caregiving system is triggered when the parent perceives a situation as frightening or stressful for the child, such as when the child signals discomfort (George & Solomon 2008). In healthy infants, differences in parents' early caregiving are related to emotional regulation, such as crying and sleeping patterns (St James-Roberts et al 2006), pain-related distress (Din et al 2009) and heart rate variability and interaction responsiveness (Kaplan et al 2008). Moreover, the parent's emotional ability to respond to the child's needs has been linked to the quality of the attachment pattern and the child's psychosocial development (Bowlby 1988; Carlson 1998; George & Solomon 1996; 2008; Shaw et al 2000). Mary Ainsworth (1978) suggested that secure attachment depends upon the caregiver's sensitivity, acceptance and psychological availability. Accordingly, George and Solomon (1996) have suggested three quality dimensions of caregiving, i) the caregiver's willingness to respond, ii) the effectiveness of caregiving strategies and iii) the ability to read and understand the child's signals.

It has been recognized that the effects of childbirth experiences, such as the experience of PTB, on the caregiving system, have not been sufficiently evaluated (George & Solomon 2008). In particular, the experiences and the consequences for parents' caregiving of infants born late preterm have been sparsely investigated. Furthermore, studies that focus on fathers' caregiving system are lacking.

Parental health and caregiving problems

The transition to parenthood is often a time for positive expectations and development. However, there are also frequent reports of mental health problems in new parents (reviewed for example in Gavin et al 2005 and Paulson & Bazemore 2010). Mental health problems in parents could influence the quality of parental functioning and thereby the future health of the child (Hay et al 2008; Korja et al 2008; Luoma et al 2001; Ramchandani et al 2008; Treyvaud et al 2010; Zelkowitz et al 2009). There are many factors that might complicate the psychological well-being of new parents. Such factors include low socioeconomic status, single parenthood and lack of social support as well as disease, developmental or sleeping problems in the offspring (Leigh & Milgrom 2008; Sepa et al 2004; Östberg et al 2007). As mentioned, having an infant born preterm could also involve difficulties for new parents.

Previous research on parents' with preterm infants has mostly focused on mothers and particularly on mothers with infants born very preterm. These studies have reported that mothers might react with depression (Davis et al 2003b; Feldman & Eidelman 2007; Miles et al 2007), anxiety (Gennaro 1988), general mental health problems (Treyvaud et al 2010) or stress (Younger et al 1997). Mothers of preterm infants have also been shown to be at increased risk of developing exaggerated controlling behavior in relation to the infant (Forcada-Guex et al 2006; Muller-Nix et al 2004). Early gestational age, low birth weight, infant illness or disability and experienced lack of social support have all been associated with continuous depression after PTB (reviewed by Vigod et al 2010). Yet, there are also contradicting findings of mothers of infants born very preterm who do not show higher rates of mental distress (Gray et al 2011; Scheiner et al 1985; Tommiska et al 2002).

The physical health consequences for mothers of preterm infants have been sparsely evaluated and findings are inconclusive. There are some reports indicating that mothers of infants born extremely preterm suffer more from physical symptoms than mothers of term infants (Stjernqvist 1992) also over a long period of time (Haas & McCormick 1997). Moreover, mothers of very-low-birth-weight infants have shown poorer immune function (decreased lymphocyte proliferation) compared to mothers of term infants at 1, 2, and 4 months post partum (Gennaro et al 1997). In another study by Gennaro and Bloch (2005) no difference was found in self-reported health between mothers of preterm and term infants. In a recent study on mothers with infants admitted to a neonatal intensive care unit (NICU), mothers reporting high stress also showed higher levels of pro-inflammatory markers

(Howland et al 2011). Regarding fathers' health, Stjernqvist (1992) found no difference in self-reported physical symptoms between fathers of preterm and term infants. Immunological parameters have not been thoroughly studied in fathers of preterm infants.

Fathers' involvement in the early caregiving of infants has been changing during the latest decades and the understanding of contemporary fatherhood might vary (Draper 2003) and could include viewing the father as the breadwinner or as a caregiver equal to the mother (Johansson 2011; Seward et al 2002). Research on fathers of preterm infants also shows conflicting results. Some studies have reported that fathers of infants born preterm demonstrate a high degree of early engagement (Fegran et al 2008; Lindberg et al 2008), while others suggest that fathers experience a lack of control, delayed bonding with the infant and role conflicts between parental demands and the claims of the external environment (Arockiasamy et al 2008; Lundqvist et al 2007; Sullivan 1999). Some studies indicate that fathers experience less stress than mothers when having an infant born preterm (Lau & Morse 2003; Miles et al 1992) while others report no differences in the stress levels of mothers and fathers (Jackson et al 2007; Kaaresen et al 2006).

The healthcare settings where preterm infants are cared for have also changed a lot in recent decades. In Sweden, many NICUs have implemented the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) that besides individualizing the infant care also emphasizes the parents' role as caregivers (Westrup 2007). Moreover, kangaroo care, where preterm infants are carried skin-to-skin by the mother or father, has been recommended for both low-income and high-tech settings (Nyqvist et al 2010; WHO 2003).

In a study from the Netherlands, fathers of infants cared for according to NIDCAP reported higher stress than fathers of infants in basic care. The authors argue that the increased involvement of fathers also contributed to increased parental stress (van der Pal et al 2007). Swedish fathers often take part as caregivers already after the birth (Waldenström 1988) and they might therefore be at elevated risk of mental distress in early parenthood.

Etiology of PTB

Despite the improvements in neonatal care and thereby the increased survival rates of preterm infants, both research and clinical practice are still struggling to reduce the incidence of PTB. The lack of knowledge of the full etiology makes this struggle difficult. Today, there is consensus on the etiology of preterm delivery as being complex and multifactorial. There are different obstetrical conditions leading to PTB, mainly divided into two groups: i) spontaneous PTB after preterm labor or preterm prelabor rupture of fetal membranes (PPROM) and ii) idiopathic or medically indicated PTB by cesarean section or induction of the delivery for maternal or fetal indications (such as preeclampsia or fetal growth retardation). Spontaneous PTB constitute about 70% of all PTB (Goldenberg et al 2008). Spontaneous PTB as well as preeclampsia, the main diagnosis in idiopathic PTB, might have overlapping etiologies including an inflammatory pathway (Orsi 2008).

There are several risk factors identified for PTB, and many are common for both idiopathic and spontaneous PTB. Risk factors identified could be divided into i) maternal risk factors, ii) reproductive risk factors and iii) risks associated with pregnancy characteristics. Maternal risk factors include, among others, high or low maternal age, low or high body mass index (BMI), low socioeconomic status and single marital status (Goldenberg et al 2008). Women who previously delivered preterm are at increased risk for recurrent PTB. Additionally, previous miscarriage and previous induced abortion as well as subfertility are associated with a higher risk for PTB (Axmon & Hagmar 2005; Swingle et al 2009). Pregnancy risk factors include, for example, multiple gestation and pregnancy through assisted reproductive technology (ART), smoking, intrauterine infection and medical disorders such as diabetes or hypertension (Goldenberg et al 2008). Despite an increased understanding of the etiology of PTB, the majority of PTB remain unexplained.

Psychosocial factors contributing to PTB

There is a growing body of evidence suggesting that psychosocial factors play a role in the etiology of PTB (Christian 2011; Orr & Miller 1995; Schetter 2011). Psychosocial factors seem to increase not only the risk of spontaneous PTB, but also the risk of developing pathology associated with medically indicated PTB, such as preeclampsia (Kurki et al 2000; Qiu et al 2009).

Stress

It has been suggested that increased maternal stress during pregnancy is related to PTB (Glynn et al 2008), and conversely that reduced stress levels during the second trimester are associated with longer gestation (Ruiz et al 2001). A recent review stated that elevated stress causes 1.5 to 3-fold increased risk of PTB (Christian 2011).

There is no consensus about when the stress exposure during pregnancy could be most harmful. Recent studies have indicated that stress in the first half of pregnancy (Roy-Matton et al 2011) or in the 5^{th} or 6^{th} month (Class et al 2011) could be considered the worst regarding risk of PTB. However, there are also studies reporting no associations between stress and PTB (Krabbendam et al 2005; Lobel et al 2000).

Depressive symptoms and affect

For negative emotions, such as negative affect/lack of positive affect and depressive symptoms, there are diverse findings, although increasing evidence indicates an association between clinical depression or depressive symptoms and PTB (Dayan et al 2006; Grote et al 2010; Li et al 2009; Lobel et al 2000; Neggers et al 2006; Orr et al 2002). Among studies that did not support such an association is a Swedish study on 1465 pregnancies, in which no significant relationship was found (Andersson et al 2004). Also studies by Messer et al (2005) and Copper et al (1996) did not confirm the suggested association between depressive symptoms and PTB.

Some studies regarding psychosocial risk factors have indicated an interaction effect between stress/depressive symptoms and BMI with an elevated risk of PTB in women with both psychosocial strains and low BMI (Dayan et al 2002; Neggers et al 2006).

In addition to studies on stress and depressive symptoms, there has been research indicating an impact on the risk of PTB from poor social support (Orr 2004), unplanned pregnancy (Orr et al 2000) and anxiety/panic disorder (Chen et al 2010; Orr et al 2007). Furthermore, it has been suggested that severe mental disorders such as psychosis increase the risk of PTB (Lee & Lin 2010; Matevosyan 2010). Within the growing body of evidence for psychosocial contribution to PTB, a connection via the inflammatory pathway has been proposed (Christian 2011; Coussons-Read et al 2005; Wadhwa et al 2001).

Reproductive immunology

The immune system is the body's cellular and molecular defense, its purpose being to protect the body from threats such as bacteria and viruses and to eliminate damaged and altered cells. The immune cells are distributed throughout the tissues, the bloodstream and in the lymphoid organs. The coordinated reaction of the cells and molecules through which the immune system functions in response to threats is called the immune response. Inflammation is part of this response - necessary in fighting off pathogens and/or in wound healing. Moreover, the immune response is crucial for pregnancy to occur.

Central to inflammation is the recruitment of immune cells to sites where elimination of threat or repair of damage should take place, or in the case of implantation, to promote an adhesive capacity in the uterine cavity. This recruitment is mediated through cytokines and chemokines. These are small proteins that are released by immune and other cells, and they can act as recruiters of immune cells from the circulation and activate and regulate cell functioning to enrich certain immune cell sub-populations. Cytokines can function both on local and systemic levels. There are many (about a hundred) identified cytokines and chemokines. Labels of cytokines include interleukin (IL), interferon (IFN) and growth factors and they could be classified as pro-, anti-inflammatory or regulatory depending on their effect on target cells. During embryonic implantation, there are many cytokines, chemokines and growth factors secreted into the uterine cavity where they act both on the blastocyst and on the endometrial surface (Hannan et al 2011). Furthermore, immune cells control the orientation of the embryo and enable the establishment of the placenta through modulation of cytokine expression (van Mourik et al 2009). Dysfunctions in cytokine production might result in reproductive problems, such as miscarriage or preeclampsia (Hannan et al 2011).

The immune system has two main components; i) the innate immunity that constitutes an immediate defense against infections, although with restricted specificity and no memory formation and ii) the adaptive immunity that has a delayed but highly diverse and specific response, which develops immunological memory. The branch of innate immunity with e.g. the natural killer cells is thought to be up-regulated in pregnancy (Luppi 2003).

Adaptive immunity relies on two major cell types: i) the B cells, which primarily participate in humoral responses by producing antibodies and ii) the T cells, which are key players in cellular immunity. The T cells are divided into cytotoxic T cells (important for defense

against intracellular pathogens) and helper T (Th) cells. T cells are located in both the cervix and the uterus (Hickey et al 2011). Following implantation, the immune system needs to induce maternal tolerance to the genetically "semi-foreign" (semi-allogenic) fetus. This process requires a down-regulation of the maternal immune system. In particular, the adaptive immune function with the cytotoxic T cells needs to be controlled in order to protect the fetus (Warning et al 2011).

The Th cells are major cytokine producing cells. Originally, two different Th populations were described, Th1 and Th2. Th1 cells produce for example the pro-inflammatory cytokine IFN-γ and are important in supporting cell-mediated defenses, while Th2 cells produce mainly anti-inflammatory cytokines that are believed to favor humoral immunity. Successful pregnancy, and maternal-fetal tolerance in particular, was previously regarded as a Th2 phenomenon, while Th1 cytokines were believed to be harmful (Raghupathy 1997; Wegmann et al 1993). This notion has been questioned and later research has shown that pregnancy requires a balanced activity of both Th1 and Th2 (Mjösberg et al 2010).

More recently, other Th cell subpopulations have been described. Th17 cells are thought to be distinct from Th1 and Th2 and are important for the induction of inflammation. Another subset of T cells is the regulatory T cells (Treg) which have immunosuppressive and regulatory functions that are important in the development of immunological tolerance to the embryo (Mjösberg et al 2010). It has been stated that a balance between Th17 and Treg is important for immune homeostasis (Kimura & Kishimoto 2010a). A Th17/Treg balance is also thought to be of importance in pregnancy, as is the Th1/Th2 balance and there have even been suggestions of a Th1/Th2/Th17 and Treg paradigm (Saito et al 2010).

Inflammatory responsiveness is shown to increase towards the end of normal pregnancy (Brewster et al 2008). For instance, production of pro-inflammatory cytokines IL-6 and IL-8 (or CXCL8) is enhanced in the cervix at term pregnancy (Malmström et al 2007) and during cervical ripening there is a large increase in these cytokines (Sennström et al 2000). Similar findings have been reported in preterm cervical ripening (Dubicke et al 2008; Törnblom et al 2005). IL-6 is produced by Th2 cells but also by many other cells and is thought to have an essential function in generating Th17 cells from naïve T cells (Kimura & Kishimoto 2010b). IL-8 is part of the innate immune system and is involved in the recruitment of immune cells to sites of inflammation (Waugh & Wilson 2008). The Th 17 cytokine IL-17

can induce production of IL-8 (Kolls & Lindén 2004). Cytokines are also thought to mediate the hormones involved in uterine contractility (Mendelson 2009).

Psychoneuroimmunology

Studies within the field of psychoneuroimmunology have contributed to knowledge about the psychosocial origins of physical disease through modulated immune function. Inflammation and cytokines have been described to have putative roles in both stress-related physical disease and in psychopathology. When a person experiences psychological stress, this could initiate a stress response with activation of two major pathways: i) the hypothalamic-pituitary-adrenal (HPA) axis resulting in a release of cortisol, a glucocorticosteroid, and ii) the sympathetic branch of the autonomic nervous system (ANS) resulting in a release of adrenaline. This response is aimed at maintaining homeostasis (O'Connor et al 2000). The HPA axis, as well as the ANS activity, also involves a conversation with the immune response to enhance or suppress immune activity which in turn may modulate the risk of disease (Ader et al 1995; Heijnen 2007; Johnson et al 2005; Tracey 2002). The communication between the stress systems and the immune system is bidirectional. Accordingly, during an immune reaction, the release of cytokines not only regulates the immune response, but also triggers the stress response, see figure 2.

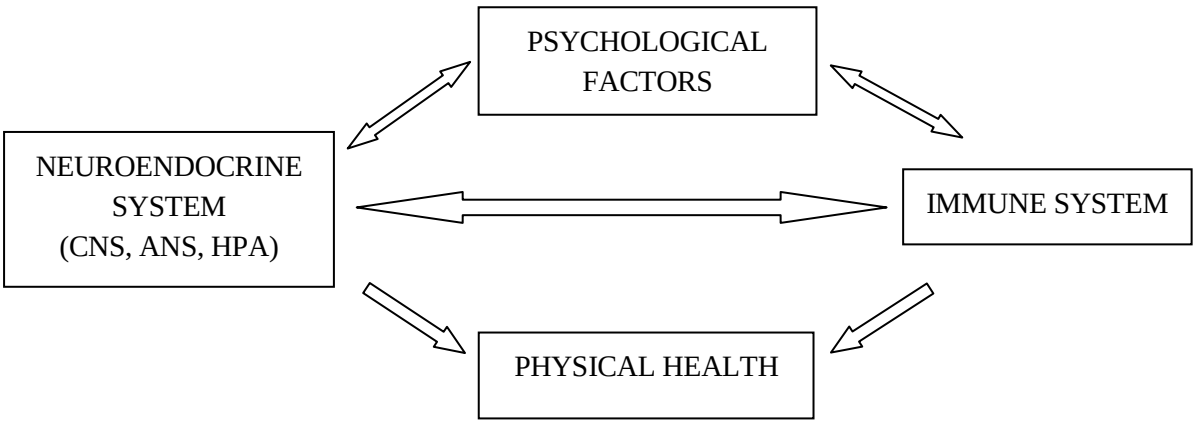

Figure 2. Associations studied within Psychoneuroimmunology, adapted from Lekander 1996.

There are several pathways for cytokines to signal to the brain. Cytokines can bind to receptors on peripheral nerves distributed in the tissues of the body and can also signal directly to the brain, for instance, small amounts of cytokines are thought to pass the blood-

brain-barrier (Hopkins 2007). It has also been shown that, besides the activation of the stress systems, cytokines modify activity of the central nervous system (CNS) and thus have a direct impact on behavior and emotions. Consequently, physical health or health problems may influence psychological well-being. For example, human experiments have shown that subjects induced with small amounts of bacteria (endotoxin) react with mood change, such as increased anxiety (Eisenberger et al 2010; Reichenberg et al 2001).

It has been suggested that the stress-related release of glucocorticosteroids induces a predominance of Th2 over Th1 (Elenkov & Chrousos 1999; Olgart Höglund et al 2006). However, acute stress has also been related to a moderate increase of pro-inflammatory markers (Steptoe et al 2007). In addition, despite the potent anti-inflammatory effects of cortisol, pro-inflammatory cytokines can be elevated in long term stress (Avitsur et al 2009). This indicates impaired HPA-axis-immune crosstalk, possibly due to blunted HPA activity. Accordingly, long term stress is suggested to cause resistance in glucocorticoid binding, which in turn could facilitate pro-inflammatory pathways (Miller et al 2008). Moreover, long term stress has been associated with elevated inflammatory activity and vulnerability to infection (Godbout & Glaser 2006; Segerstrom & Miller 2004).This process could also increase the risk of developing anxiety and depression (Kendler et al 1999; van Praag 2004). Similar to long term stress, depression has been associated with HPA axis dysfunction (Pariante & Lightman 2008) and increased inflammatory activity (Kiecolt-Glaser & Glaser 2002).

Circulating cytokines in stress and negative emotions

Levels of cytokines in the blood circulation have been suggested as a functional indicator of health and disease. For example high levels of IL-6 have been associated with an increased risk of heart failure, while regular physical activity has been associated with a reduction of IL-6 levels (Kalogeropoulos et al 2012). Moreover, stress has been related to increased peripheral levels of IL-1β and IL-6 in particular (Godbout & Glaser 2006; Steptoe et al 2007). IL-6 has a wide range of functions in immune regulation and inflammation but is regarded as mainly pro-inflammatory. IL-6 is also identified as a key player in immune to brain communication during inflammation (Hopkins 2007).

Negative mood, such as depressive symptoms, negative affect (NA), dispositional pessimism or low positive affect (PA), has been associated with higher concentrations of e.g. IL-1 and IL-6 in the circulation of both women and men (Denollet et al 2003; Dowlati et al 2010;

Kiecolt-Glaser & Glaser 2002; O'Donovan et al 2009; Wright et al 2005). Depression and NA has additionally been linked to elevated serum concentrations of chemotactic cytokines/chemokines and adhesion molecules (Rajagopalan et al 2001) and higher stimulated levels of chemotactic IL-8 (Marsland et al 2007). Interestingly, people experiencing successful treatment with antidepressants demonstrate a decrease in pro-inflammatory cytokine levels (Janssen et al 2010).

In line with findings concerning elevated pro-inflammatory markers in depression, depressive symptoms have been associated with lower levels of regulatory/anti-inflammatory IL-10 and IL-13 (Dhabhar et al 2009; Eskandari et al 2007). IL-10 is a major regulatory cytokine, released by Treg cells among others and is thought to have a suppressing effect on pro-inflammatory cytokines (Sabat et al 2010) and IL-13 is suggested to induce the development of Treg from naïve T cells (Skapenko et al 2005). In summary, the notion of the associations between psychosocial factors and inflammatory markers could be useful in the understanding of the mechanisms involved in PTB.

Circulating cytokines during pregnancy and delivery

Maternal levels of circulating cytokines during pregnancy have been linked to the risk of PTB. Murtha et al (1998) found that women who delivered preterm had elevated circulating levels of IL-6 at 22-34 weeks of gestation. Similarly, Vogel et al (2007) showed that high serum levels of several pro-inflammatory cytokines, including IL-6, IL-8 and IL-18 during the second trimester predicted spontaneous PTB. Somewhat contradictory to this, Ekelund et al (2008) found that women with low levels of IL-18 and high levels of IL-12 had a twofold increased risk of spontaneous delivery before 34 weeks of gestation. In mice, a lack of IL-18 has been associated with a higher frequency of fetal loss (Wang et al 2006).

Anti-inflammatory cytokines have been studied less than pro-inflammatory agents in relation to pregnancy. However, IL-4 and IL-10 have been found in higher concentrations in the cervix of women with preterm than women with term labor, suggesting that anti-inflammatory markers could be involved in the pathogenesis of preterm labor (Dubicke et al 2010). Moreover, primate models show that infusion with IL-10 significantly reduces IL-1β induced uterine contractility (Sadowsky et al 2003), which could indicate an important function of Treg cells. Polymorphism in genes related to anti-inflammatory cytokines, e.g. IL-13, has been observed in one study on preterm infants (Heinzmann et al 2009).

In late pregnancy, IL-6 and IL-8 production is enhanced in the cervix as previously mentioned (Malmström et al 2007) and, during labor, elevated levels of IL-6 and IL-8 are also seen in circulation (Ida et al 2000; Malamitsi-Puchner et al 2005; Rizos et al 2005).

There are hypotheses concerning a fetal role in delivery onset (Mendelson 2009). It has been suggested that an inflammatory reaction of the fetus, called the fetal inflammatory response syndrome (FIRS) and characterized by elevated levels of IL-6, is involved in PTB (Gotsch et al 2007). In line with this hypothesis, Skogstrand et al (2008) found elevated levels of e.g. IL-6 and IL-8 and lower IL-18 in dried blood spots from neonates born preterm compared to those from infants born at term. The authors reason that a combination of fetal, placental and maternal inflammation could be part of PTB pathogenesis.

Psychoneuroimmunology and PTB

In spite of the growing evidence for psychological risk factors for preterm delivery and hypotheses of inflammation as a mechanism involved, studies that aim to link psychosocial factors with inflammation are still scarce within the research field of PTB. Nevertheless, throughout pregnancy; from the controlled inflammation required at implantation through the development of maternal-fetal tolerance, to the onset of delivery, there could be disturbances of the immune function due to infection, physical strain, malnutrition or psychological factors, see figure 3.

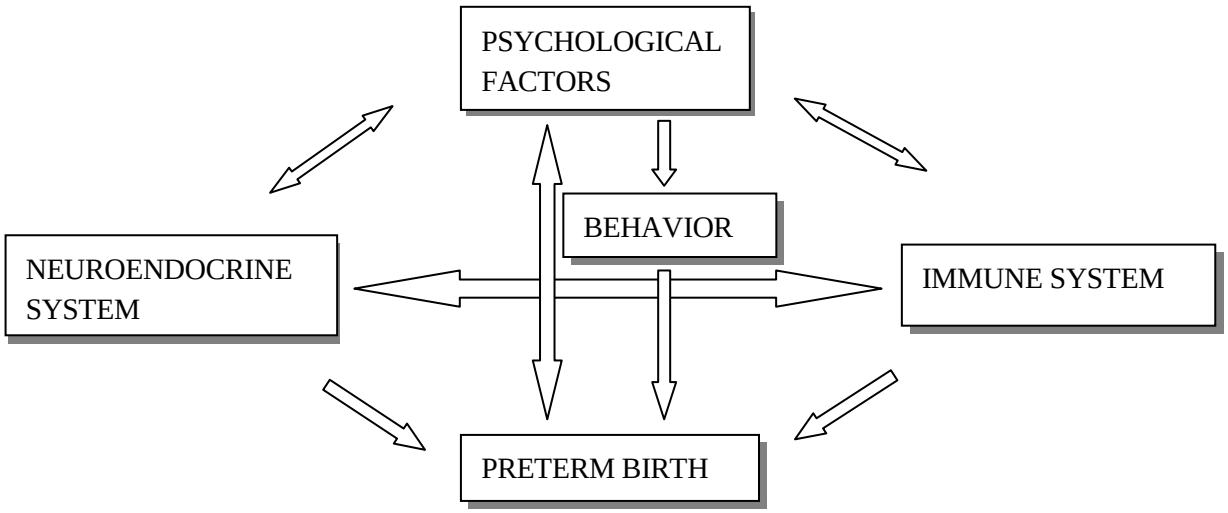

Figure 3. Psychoneuroimmunology, applied to PTB research.

Previous research has indicated that the link between psychosocial factors and immune function is evident also during pregnancy. Stress has been associated with elevated levels of pro-inflammatory markers and lower levels of IL-10 in pregnant women (Coussons-Read et al 2005). Additionally, stress has been shown to predict higher stimulated levels of IL-1β and IL-6 in blood samples from women in late pregnancy (Coussons-Read et al 2007). However, while Christian et al (2009) reported a significant positive relationship between depressive symptoms and IL-6 in pregnant women, they found no relationship between perceived stress and inflammatory markers. Mattes et al (2009) found associations between mothers' antenatal depressive symptoms and increased production of e.g. IL-6 and IL-10 in the umbilical cord blood.

When considering the challenge of understanding the complexity of PTB, the influence of inflammation should be viewed in the context of psychosocial health and vice versa (Christian 2011; Ruiz & Pearson 1999).

Knowledge gaps in PTB research

In summary, the need for further studies within the field of PTB has been stated. There have been contradictory reports regarding the potential risk for women with depressive symptoms to deliver preterm. Moreover, even though there have been a few attempts to apply the knowledge from psychoneuroimmunology to the research on psychosocial risk factors for PTB, there is still a great need for further understanding about the underlying mechanisms. Another area that has not been fully explored is the relationship between PTB and parents' experiences and psychobiological health during the transition to parenthood. In particular, parental experiences and early caregiving after late PTB has not been studied and moreover, fathers' experiences, caregiving and well-being after PTB have not been fully elucidated.

AIM OF THE THESIS

The overall aim of this thesis was to study PTB from different perspectives to gain further understanding of the psychosocial contribution to the etiology of PTB, of a possible inflammatory pathway for the psychosocial contribution, and to gain further knowledge regarding the consequences of PTB for parents' health and experiences of caregiving.

The specific aims were:

- To investigate whether antenatal depressive symptoms increase the risk for PTB. (I)

- To investigate whether affectivity variables differ between mothers with preterm and term births and if serum levels of pro- and anti-inflammatory cytokines differ in maternal and umbilical cord samples from preterm and term births, respectively. Finally, to study if there is an association between mothers' affectivity and levels of maternal and umbilical cord serum cytokines. (II)

- To explore first time mothers' and fathers' experiences of PTB with infants born early or late preterm with regard to the development of caregiving. (III)

- To investigate levels of and associations between perceived stress and circulating IL-6 i) after the birth and ii) at infant age four months, in parents of preterm infants in comparison to parents of full term infants. Finally to explore possible predictors for high stress levels in mothers and fathers of preterm infants at infant age four months. (IV)

METHODS

All studies in this thesis were performed in Sweden, with participants in antenatal, delivery, post-partum and neonatal care. Study I was based on a national Swedish survey on women's experiences of childbirth, whereas studies II-IV were based on a clinical sample of families with PTB and term birth (TB).

Table 1. Overview of participants included and methods used in studies I-IV.

	Study I	**Study II**	**Study III**	**Study IV**
Participants	2904 women	27 mothers with spontaneous PTB; 37 mothers with spontaneous TB	10 mothers, 10 fathers with early PTB; 9 mothers, 8 fathers with late PTB	38 mothers, 36 fathers with PTB; 40 mothers, 37 fathers with TB
Parity	Primi- and multiparous	Primi- and multiparous	First time parents	First time parents
Data collection methods	Questionnaire; Self-rating scales; SMBR	Questionnaire; Self-rating scales; Medical records; Interview	Medical records; Interview	Questionnaire; Self-rating scales; Medical records
Time for data collection	Pregnancy (mean 16 weeks pregnant)	Delivery	First week post partum	First week post partum; Infant age four months
Psychosocial factors (method)	Depressive symptoms (EPDS)	Depressive symptoms (Interview); Positive and negative affect (PANAS)	Experiences (Interview)	Perceived stress (PSS)
Blood samples		Mothers, umbilical cord		Mothers, fathers
Analyzed cytokines (quantification method)		IL-1α, IL-6, IL-8, IL-10, IL-13, IL-18, IFN-γ (Bio-plex)		IL-6 (ELISA)
Method for analysis	Logistic regression	T-test; Chi-2; Linear regression; Pearson's test of correlation	Qualitative content analysis	T-test; Chi-2; ANOVA; Spearman's correlation; Logistic regression

Procedures and participants, study I

Study I is based on selected data from a national Swedish survey on women's experiences of childbirth, see figure 4. The study sample was drawn from the total population of pregnant women and recruited at their first booked visit to antenatal health clinics during three recruitment weeks distributed over one year (May and September 1999, and January 2000). Of all antenatal clinics in Sweden, 97.5% chose to participate in the study. The only exclusion criterion for women was inability to understand Swedish. A total of 3061 women (67% of eligible women) completed the questionnaire that included questions on socio demographic characteristics, smoking habits, reproductive history and depressive symptoms. Data on gestational length was extracted from the Swedish Medical Birth Register (SMBR), based on the best available estimate, which in most cases is ultrasound.

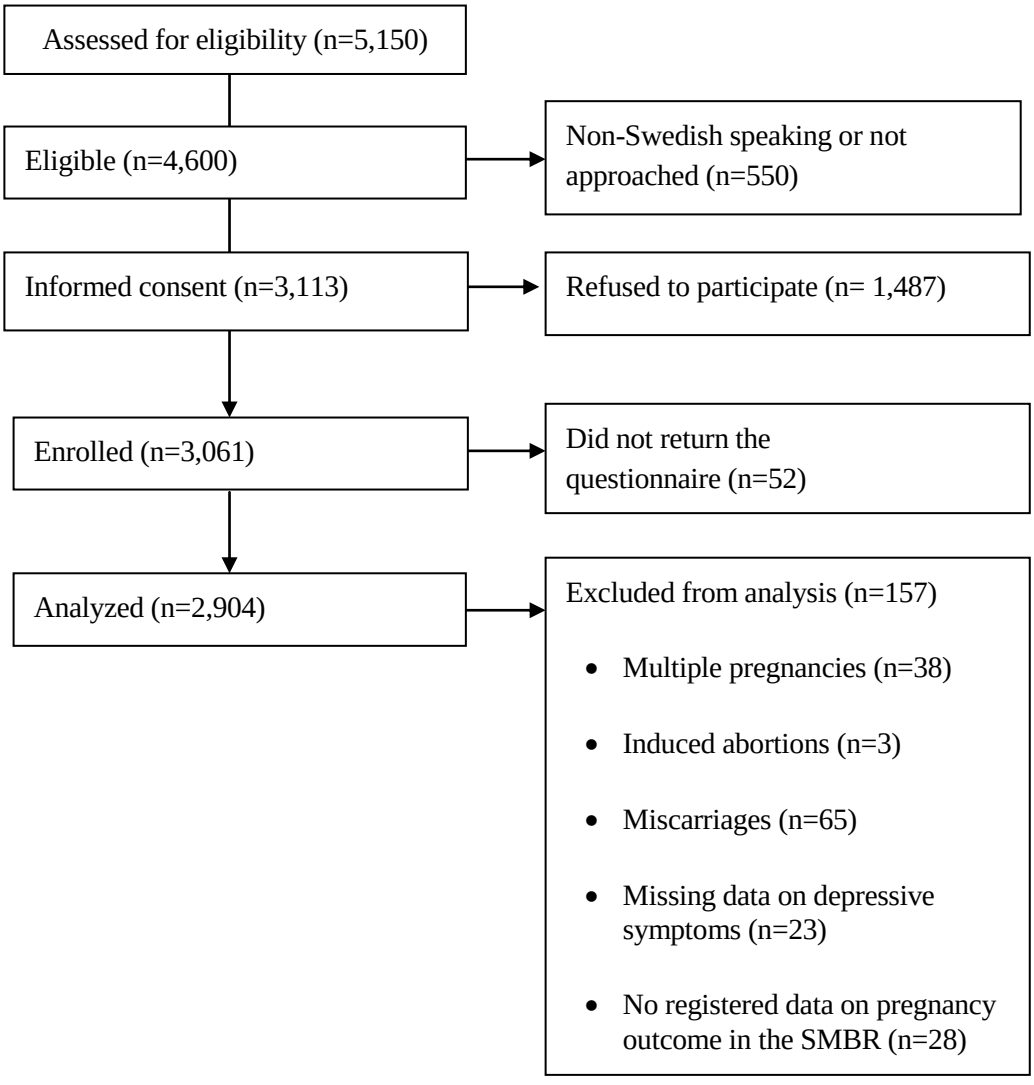

Figure 4. Flow chart of participants in the study I.

The study sample in study I included 2904 women. The average length of gestation at the time for completion of the questionnaire was 16 weeks (standard deviation (SD) = 3.4). Mean age of the women included was 29.4 years (range 17-46, SD=4.7), 42.7% of the women were primiparous, 90.5% were born in Sweden, 10.6% smoked in early pregnancy and 2% had conceived through assisted reproductive technology. There were considerable similarities between the study sample and the cohort of all 84 729 women who gave birth in Sweden in 1999. An expected difference, due to the language exclusion criterion, was that a larger proportion (90.5%) of the women in the study sample was born in Sweden, compared to 82% in the 1999 cohort.

Procedures, studies II-IV

Families were enrolled at the Karolinska University Hospital, Solna, Sweden during 2007-2008. The participating women and men were given written and oral information about the study, ideally when the mother was admitted to hospital for the birth of their infant, either preterm or at term, and they gave their consent before the birth. However, 22 of the participating families were informed about the study and/or gave their consent to participate after the birth.

To be eligible the parents had to be ≥ 18 years old and able to communicate in Swedish. Inclusion criteria for the women were: primiparity with spontaneous delivery onset and delivery after 23-35 completed weeks of gestation (preterm group) or delivery after 38-41 completed weeks of gestation (term group). Exclusion criteria for the mothers were: multiple gestation, preeclampsia, diabetes or other systemic disease during pregnancy or fetal malformation. To increase the sample size, also women who delivered their second child were recruited during the last months (n=8). However, multiparous women were only included in the first data collection (study II) and not in the follow-up. Fathers were asked to participate only if the mother agreed to do so. Women with preterm delivery and their partners were included consecutively, however this was limited to when someone from the research team was present. Approximately 75% of the families approached agreed to participate. Following enrollment of women with preterm delivery, eligible women with term delivery and their partners were approached and given information about the study and about 50% agreed to participate. All participants gave their written consent.

The clinical settings for studies II-IV were mainly three hospitals in Stockholm County, Sweden. Families who delivered at term were cared for at the delivery and post-partum wards. First-time mothers usually stayed in the hospital for two days or more post partum. In the preterm group, some mothers were hospitalized before the delivery at the antenatal ward and in these cases the fathers were most often offered the possibility of an overnight stay. Post partum, infants born early preterm were cared for in the NICU level III (specialized for critically ill infants and infants born very preterm). Mothers initially stayed in the postpartum ward and often it was possible for fathers to stay overnight. Settings postpartum changed over time as infants got better or worse or were moved to new hospitals. Infants born after 34-35 weeks of gestation were usually roomed-in with the mothers at the postpartum ward and most fathers had the possibility to stay overnight. A few of the infants born late preterm were cared for in the NICU, level II (special care nursery), with family-centered care.

Data collection started ideally during the delivery with blood sampling of the mother and father. After the birth, umbilical cord blood was obtained. The mothers were blood sampled a second time after 24-72 hours after the birth. However, some families were enrolled after the birth and blood samples were then only taken post partum from the mother and father. Information on background data was collected using questionnaires that were administrated individually to the mother and father early during the postnatal hospital stay. If a family with a preterm infant moved to a different hospital, the data collection was continued at the new unit. The questionnaires also included several self-report measurements of psychosocial well-being, as listed below. In addition, the mothers and fathers were interviewed separately at one time-point during the first week. The interview included questions on the experience of the delivery as well as questions on psychosocial well-being. Obstetrical data were retrieved from medical records.

When the infant was aged four months (corrected age for preterm infants), the follow-up data collection was conducted. The parents (first-time mothers and their partners) were invited to the Karolinska University hospital where blood samples were collected again and the mothers and fathers were interviewed separately. Three families declined to come to the hospital and the follow-up was then conducted in their homes. A follow-up questionnaire including self-report measurements was also administrated and filled out individually by the parents.

Participants, studies II-IV

For an overview of the participants in studies II-IV, see figure 5.

Women during delivery (II)

Participants were included in study II if there were available data on cytokine levels from the delivery. In the preterm group, 8 women gave birth at 24-27 completed weeks of gestation, 5 women at 30-33 weeks and 14 women at 34-35 completed weeks of gestation. The term group consisted of 37 women with delivery at 38-41 completed weeks of gestation. In total 8 women in this study were multiparous; 5 in the PTB group and 3 in the term group. Eleven women in the preterm group who delivered at gestational week 24-33 received corticosteroid treatment (betamethasone) before delivery to improve fetal lung maturation.

Mothers and fathers of preterm infants (III)

Participants were chosen from the group of parents with preterm infants using stratified sampling (Krippendorff 2004) in order to include parents of early as well as late preterm born infants. The selection of participants also aimed at acquiring interview material that was appropriate for qualitative analysis, i.e. to get narratives with rich descriptions. The study group comprised 37 parents of infants born early and late preterm (in the 24^{th} -30^{th} week of completed gestation or in the 34^{th}-35^{th} weeks of completed gestation).

Mothers and fathers with infants born preterm and term (IV)

This study included first time mothers and fathers who participated in the follow-up at infant age four months (corrected age for preterm infants). The preterm group consisted of 38 mothers and 36 fathers of preterm infants. The term group consisted of 40 mothers and 37 fathers of term infants.

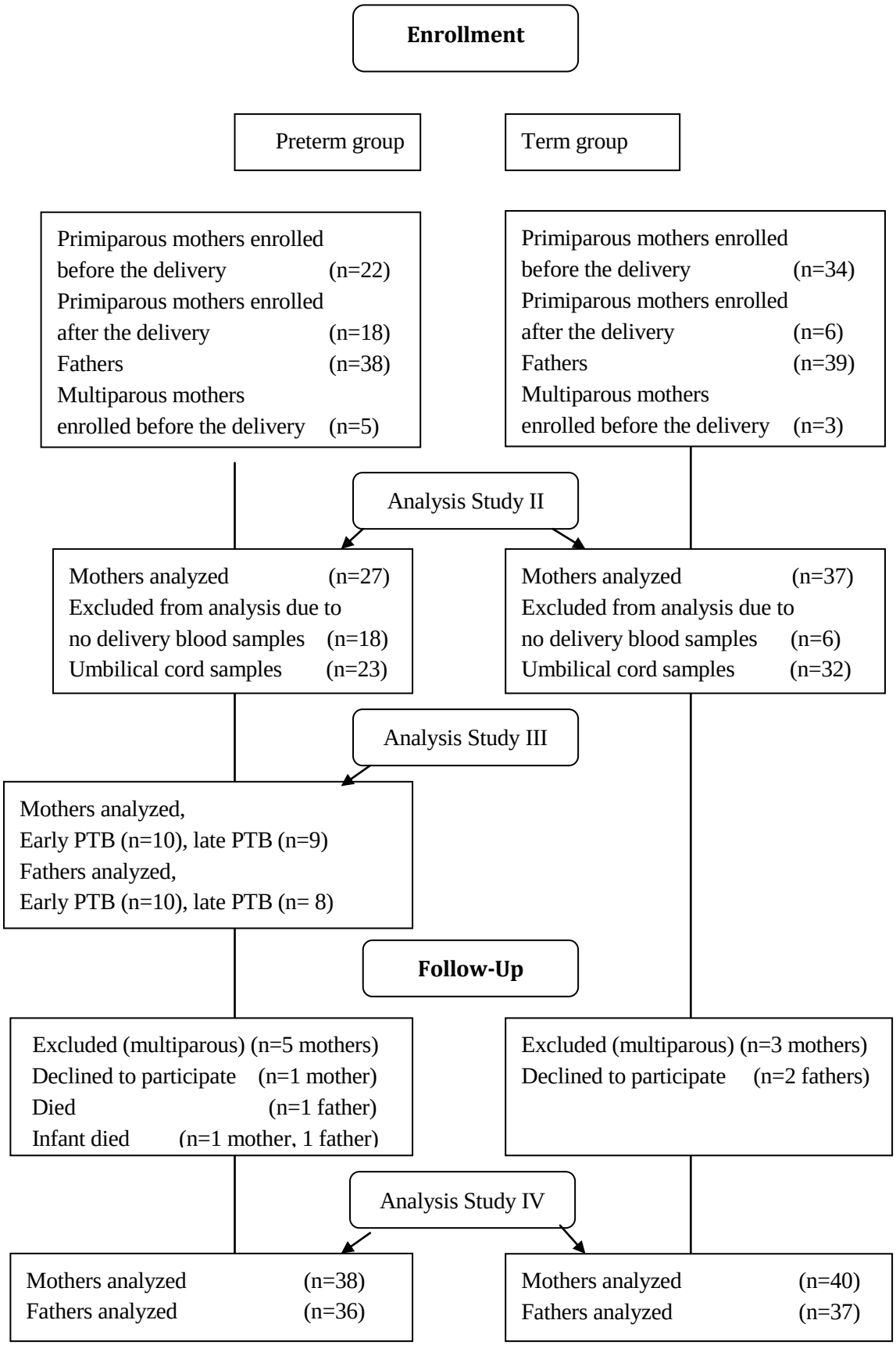

Figure 5. Enrollment and follow-up of the participating mothers and fathers in Studies II-IV.

Self-report measurements

The Edinburgh Postnatal Depression Scale (EPDS) (I)

The Edinburgh Postnatal Depression Scale (EPDS) is a ten-item self-report scale designed to screen for post-partum depression (Cox et al 1987) but it has also been validated and used for antenatal samples EPDS (Murray & Cox 1990). The EPDS includes questions on depressed mood and symptoms over the past seven days. Each item is assessed on a four-point Likert-like scale and the total score ranges from 0 to 30. In study I the cut-off level 11/12 was used, where participants who scored ≥ 12 were categorized as having depressive symptoms, in accordance with a Swedish validation study (Wickberg & Hwang 1996). The EPDS is not a diagnostic tool, but it has shown good sensitivity and specificity in comparison with a diagnostic interview according to DSM-III-R in the Swedish validation study.

The Positive and Negative Affect Schedule (PANAS) (II)

The Positive and Negative Affect Schedule (PANAS), (Watson et al 1988), was used to measure the trait positive affect and negative affect (PA and NA) which have been identified as two distinctive components in studies of affect (Watson & Tellegen 1985). PA reflects to which extent a person feels *enthusiastic, active, alert* etc, whereas NA measures subjective distress like *shame, guilt* and *fear*. The items are rated on a 5-point scale from 1=*not at all* to 5=*very much* with a maximum score of 50 for PA and NA respectively.

Perceived Stress Scale (PSS) (IV)

The 14-item Perceived Stress Scale (PSS) was used to measure subjective experience of stress. The respondent reports to what degree he or she has appraised situations as stressful during the past month on a 5-point Likert scale ranging from 0=*never* to 4=*very often* (Cohen et al 1983). For example: "In the last month, how often have you been able to control irritations in your life?" The PSS has previously been validated and used in Sweden (Eskin & Parr 1996).

The Barnett Scale (IV)

The Barnett Scale was used to measure different aspects of the marital relationship such as communication, sharing of household tasks, friendship, love, and attraction (Barnett et al 1993). The scale consists of 15 items for which the respondents report on a 5-point Likert scale ranging from 1=*disagree totally* to 5=*agree totally*. The scale has been translated and previously used in Sweden (Hjelmstedt et al 2006).

Ages and Stages Questionnaire: Social Emotional (ASQ:SE) (IV)

We used the parent report screening tool Ages and Stages Questionnaire: Social Emotional (ASQ:SE), (Bricker et al 2004), to assess the parent's evaluation of the infant's socio-emotional development. In the questionnaire for infants 3-8 months the parent evaluated the baby's capacity and behavior in five areas: self-regulation, communication, adaptive functioning, affect, and interaction with people. For example if the baby "let you know when he/she is hungry or sick". Each item scores 0=*no problem*, 5=*sometimes a problem* or 10=*most often a problem* and 5 additional points are given if the parent reports concern about a specific problem/item. The maximum score is 285 and the suggested clinical cutoff is 45. Parental screening of social-emotional development has been shown to predict later outcomes (Briggs-Gowan & Carter 2008).

Missing values

Missing values on the EPDS, the PANAS, The Barnett Scale, the PSS and the ASQ:SE were replaced by the individual's average value on the scale/subscale, if less than half of the values were missing (Engels & Diehr 2003; Shrive et al 2006).

Assessment of depressive symptoms through interview (II)

Within the first eight days after the delivery, mothers and fathers were interviewed about the experience of pregnancy/partner's pregnancy, delivery and first contact with the infant. The interviews were semi-structured and included questions on psychological well-being. The parents were specifically asked the following question: "Did you experience depressive feelings during the pregnancy/partner's pregnancy at any time-point?" Follow-up questions were asked when necessary for clarification. Only data on mothers' depressive mood is used in this thesis (study II). Descriptions of continuous depressed mood were considered as depressive symptoms, and coded as yes/no. Descriptions of occasional depressive feelings (one day or on one occasion etc) were not included. Participants who reported depressive symptoms were asked whether they had received treatment.

Qualitative interviews (III)

A semi-structured interview (Kvale 1996) was performed separately with mothers and fathers within the first eight days after the delivery. For study III, interview data from parents with infants born preterm were used. The interviews were conducted at the hospital where the infant was admitted and the time-points for the interviews were set in collaboration with the family and scheduled to fit in with the ward routines.

The interview guide was produced through discussions in the research team and was tested in pilot interviews. Each parent was asked to recount his or her experience from the first sign of the approaching delivery until the time of the interview and to talk about their experiences of the clinical care they had received. Further, they were asked about the experience of seeing the baby for the first time and how they perceived the contact with the baby and the baby's responses. Depending on the individual interviews, follow-up questions were asked when clarification was needed. Notes were taken during the interviews and the majority of the interviews were recorded with the respondents' consent and afterwards transcribed verbatim. The duration of each interview was approximately 30 to 75 minutes.

Qualitative content analysis

Qualitative content analysis was used to analyze the interview data and the analysis was carried out in steps as described by Graneheim and Lundman (2004). Firstly, the transcribed text was read several times to get an overall sense of the interviews. Secondly, meaning units were identified i.e. parts of the text dealing with the topic of interest (experience of PTB etc) according to the aim. In the third step, the meaning units were condensed and given labels (codes) describing the interpreted content. The condensed units were sorted into categories based on similar content and grouped into sub-themes which were discussed by all the authors of study III and consecutively revised. The sub-themes identified were rechecked and compared with the individual narratives to ensure that the results mirrored the data and that no important information was missing in the sub-themes. The sub-themes were organized into two over-all themes. A reflexive attitude (Alvesson 1996; Malterud 2001) was maintained throughout the process. This implies, for instance, that attempts were made to find competing conclusions when looking at data and interpretations. Moreover, earlier empirical work and existing theories are thought to provide a basis for analysis. During the analysis, focus shifts between the previous evidence and the data collected. The empirical findings are central, while pre-understanding from the earlier theory is allowed.

Blood sampling and serum analyses (II, IV)

Blood samples from mothers were collected i) during labor, defined as cervix dilated a minimum of 4 cm and ongoing contractions (study II), ii) during daytime at 24-72h post partum (study IV) and iii) at the follow-up at infant age four months (study IV). Blood samples from fathers were collected at two time-points (study IV), i) at one time during the partner's delivery/after the birth and ii) at the follow-up at infant age four months. Samples were taken by routine venipuncture. Blood samples from umbilical cords were collected after clamping according to hospital routines. The samples were allowed to clot and were thereafter centrifuged at 2400x*g* for 10 min at 4°C. Serum was stored in aliquots at -70°C until analysis.

Bio-plex (II)

For quantification of the cytokines IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p70, IL-13, IL-17, IL-18 and IFN-γ, the Bio-Plex human cytokine assays (Bio-Rad Laboratories Inc., California, USA) were used, according to the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation were below 15 and 11% respectively for these assays. Values were computed using the Bio-Plex Manager software version 5.0. All detectable values were extrapolated from the standard curve. For the analyses, only the cytokines in which a minimum of 30% of the samples were above the limit of detection (LOD) were used. Cytokines included in analyses were: IL-1α, IL-6, IL-8, IL-10, IL-13, IL-18 and IFN-γ. (Statistical details of these cytokines are presented in table I, study II).

ELISA (IV)

For study IV, serum levels of IL-6 were determined by immunoassay, determined by enzyme-linked immunosorbent assay (ELISA), using a commercially available kit, Solid-phase ELISA, Quantikine® HS Human IL-6 Immunoassay (R&D Systems, Inc. MN, USA). A high-sensitivity kit was used, with a sensitivity of 0.039 pg/ml, the intra-assay coefficient of variation was 7.4% and the inter-assay coefficient of variation was 7.8%.

Transformation of cytokine data (II, IV)

The cytokine data were substantially skewed and were therefore log or inverse transformed prior to (parametric) analysis to provide a better approximate normal distribution. The

inversed values were then reflected to generate the correct direction of association when presenting results.

Statistical methods (I, II, IV)

Single variable comparisons (Study II, IV)

Single variable comparisons between the groups were computed using chi-square tests for categorical data and independent t-tests for continuous data.

Logistic regression (I)

In study I, logistic regression analyses were performed for bivariate analyses to estimate the risk of scoring ≥12 on EPDS as well as for the risk of PTB. Also, multiple logistic regression analysis was computed to estimate the risk of PTB associated with antenatal depressive symptoms, controlling for other known risk factors: low/high maternal age; single status; born outside Sweden; low education; unemployment in early pregnancy; previous smoking/smoking in early pregnancy; ART; previous miscarriage; primi-/multi parity and history of infertility (Axmon & Hagmar 2005; Goldenberg et al 2008; Swingle et al 2009).

In study IV, the parents in the preterm group reporting the highest PSS scores at infant age four months were identified (the upper quartile). Logistic regression analysis was performed to estimate the risk of high stress. Independent variables in the model were: parent gender, age, level of education, country of birth (Sweden/other country), gestational length in completed weeks, PSS scores at the first days after the birth, Barnett scale total score and ASQ:SE total score.

Tests of correlation (II, IV)

In study II, the two-tailed Pearson's test of correlation was used to investigate the relationship between the maternal and cord cytokines values as well as the relationship between maternal affectivity variables (positive/negative affect and depressive symptoms) and the cytokine values.

In study IV, the two-tailed Spearman's test of correlation (non-parametric) was computed to investigate the relationship between PSS total scores and original IL-6 values at early post partum and at infant age four months. Tests were performed separately for mothers and fathers.

Linear regression (II)

In study II, linear regression analyses were used to investigate differences between the preterm and term groups in maternal and cord serum cytokines. When group differences were found, multivariate regression analysis adjusted for corticosteroid treatment was performed. Moreover, to assess the associations found in Pearson's test of correlation between the affectivity variables and cytokines, a set of multiple regression analyses of affect and cytokine relationships adjusted for corticosteroid treatment were conducted.

Repeated measures ANOVA (IV)

In study IV, repeated measures analyses of variances (ANOVA) were computed for PSS total scores and levels of IL-6 using group (preterm/term) as the between-subjects factor and time (early post partum/infant age four months) as the within-subjects factor. These analyses were computed separately for mothers and fathers.

Statistical significance

In all studies (I, II and IV) *p*-values of less than 0.05 were considered significant.

Power calculations

Power calculations (studies II and IV) were conducted a priori for the cytokine analyses and showed that it was necessary to have ten participants in each group in order to detect a 25 percent difference with 80 percent power and alpha 0.05.

Ethical considerations

Participants in studies II-IV were informed and asked about participation when in a potentially vulnerable situation, i.e. the birth of their child. However, it was clearly stated that participation was voluntary and that health care and treatment at the clinic was not affected by the choice to participate or not. Only parents who gave written consent were enrolled in the study, and participants were informed about the possibility to withdraw at any time-point. If a participant was found to be in current need of psychosocial support, he or she was offered help to make contact with the clinic counselor.

Permission from the local ethics committee was obtained for all studies.

RESULTS

In the present work, we have looked into different aspects of PTB, starting with psychological risk factors during pregnancy (I), continuing with associations between psychological variables and inflammatory markers at birth (II), mothers' and fathers' experiences of early caregiving after early or late PTB (III) and the perceived stress and IL-6 in the first week post partum and at infant age four months in mothers and fathers (IV).

Antenatal depressive symptoms and risk for PTB (I)

In study I, based on a national sample of Swedish women, PTB occurred in 5.3% of the women (153/2904). Of these, 91 were spontaneous and 59 were medically indicated preterm births. In three cases data was missing on delivery onset. The mean score on the EPDS was 6.62 (SD=4.86). Of all the women, 15.7% (456/2904) scored ≥12 on the EPDS. Figure 6 shows the proportion of women scoring ≥12 on the EPDS, in relation to gestational length.

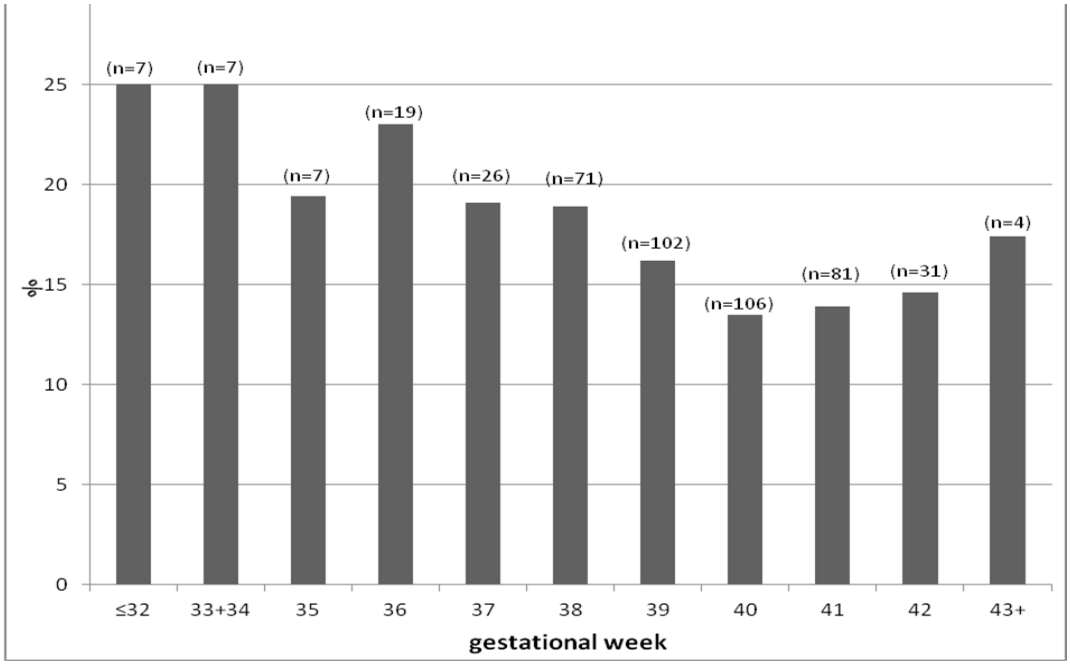

Figure 6. Proportion of women with antenatal EPDS score ≥12 in relation to gestational length at birth

In the study sample, 13 women (0.4%) reported daily use of antidepressant treatment. Two of these women gave birth preterm.

It was found that presence of antenatal depressive symptoms (EPDS ≥12) increases the risk for PTB also after adjusting for maternal and reproductive risk factors (adjusted OR=1.56, 95% CI= 1.03-2.35). The full model included the variables: maternal age, civil status, born in Sweden or not, educational level, unemployment, smoking habits, ART, previous miscarriage, parity and history of infertility, and the model significantly predicted PTB (omnibus chi-square = 24.932, df = 14, p=.035). A subgroup analysis of women <25 years showed a three-folded risk of preterm delivery among women who scored ≥12 on the EPDS (adjusted OR=3.14, 95% CI=1.37-7.19).

Affectivity and cytokines at birth (II)

In study II, there were no differences between women delivering preterm or term regarding age, education, income or pre-pregnancy BMI. Moreover, we found no differences between the two groups regarding positive affect (PA), negative affect (NA) or depressive symptoms.

Maternal levels of the cytokines IL-6, IL-8 and IFN-γ were lower in the women with preterm labor, compared to the women with term labor (p_{IL-6}=.003; p_{IL-8}=.001; $p_{IFN-\gamma}$=.046). Umbilical cord levels of IL-13 were significantly higher in the preterm group (p=.023).

Eleven women in the preterm group who delivered at gestational week 24-33 received corticosteroid treatment (betamethasone) before delivery to improve fetal lung maturation. When adjusting analyses for corticosteroid treatment, only the difference in maternal IL-8 was stable, while the differences in maternal IL-6 and IFN-γ and umbilical cord level of IL-13 were no longer significant.

In the preterm group, significant positive correlations were found between summary score of NA and maternal levels of IL-6 as well as cord levels of IL-6, IL-8, IL-10, IL-13 and IL-18, see figure 7. Positive correlations between depressive symptoms and maternal levels of IL-8 and cord levels of IL-18 were also found in the preterm group. For the term group, no significant correlations were found.

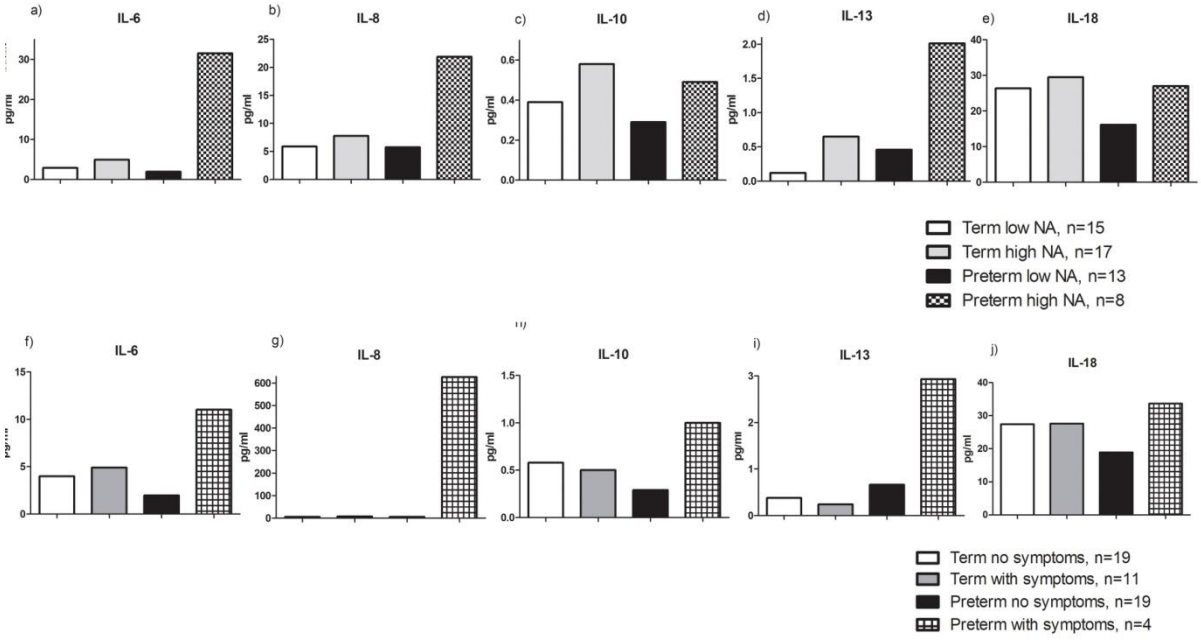

Figure 7. Median values of cord IL-6 (a), IL-8 (b), IL-10 (c), IL-13(d) and IL-18 (e) in relation to term and PTB in women with negative affect (NA) scores below or above the two groups' mean value (18.9) and median values of maternal cord IL-6 (f), IL-8 (g), IL-10 (h), IL-13(i) and IL-18 (j) in women with or without depressive symptoms.

When adjusted for corticosteroid treatment, the relationships between depressive symptoms and maternal IL-8 and between NA and maternal IL-6 remained significant (p_{IL-8}=.013, adjusted R^2=.31; p_{IL-6} =.016, adjusted R^2=.25) as well as the relationships between NA and cord levels of IL-6 and IL-18 (p_{IL-6}=.001, adjusted R^2=.52; p_{IL-18}=.023, adjusted R^2=.27) and depressive symptoms during pregnancy and cord levels of IL-18 (p=.038, adjusted R^2=.21).

Parents' caregiving of infants born early and late preterm (III)

Study III included 10 mothers and 10 fathers of infants born in the 24th-30th week of completed gestation (early preterm) and 9 mothers and 8 fathers of infants born in the 34th-35th week of completed gestation (late preterm). The mothers were aged between 22 and 39 years of age, the fathers were aged between 24 and 47 years of age. In total, 4 mothers and 1 father were born outside Sweden.

In the qualitative content analysis of the interview material, two overall themes were identified; *hindering* and *facilitating factors in the development of the caregiving*.

Early PTB - hindering and facilitating factors in the development of the caregiving

It was found that parents of infants born early preterm experienced emotional difficulties during the transition to parenthood. When facing the threat of PTB, many parents experienced a state of shock instead of looking forward to and thinking positively about the infant. After the birth, the mother and father could feel reduced to being bystanders instead of active parents and accordingly the activation of the caregiving might be delayed, especially when the infant is judged or perceived as too fragile to hold.

> "You are so helpless and there is nothing you can do. You want to hold, but you can't. [The baby] is so small. And if something happens, you can only sit and watch." (father).

However, factors that facilitate the caregiving behaviors were also reported. Parents, who had experienced holding the baby skin-to-skin (for example in kangaroo care), described this as an emotional, important and positive experience and as an important part of becoming a parent and getting to know the infant. Furthermore, when the parents were able to have faith in the progress of the infant's state and in being competent as parents, the fear and despair were lessened.

> "I believe that my touching soothes him. Because when I've been there for a long time and I've spoken [to him] in a certain way, I believe he is reacting." (mother)

The mothers and fathers of infants born early preterm seemed to go through similar processes. One exception was the role conflicts that some fathers experienced. The father's own worries for the baby and the need to support the mother were experienced as very difficult to handle alongside regular duties at work and at home.

Late PTB - hindering and facilitating factors in the development of the caregiving

Some parents with infants placed in regular post partum care expressed how they felt the staff seemed to expect them to be as other parents. The infants born late preterm are often asleep most of the time with sparse moments of alertness and contact giving, if any. Thus, the

infant's health status was experienced as difficult to assess and accordingly some mothers and fathers felt a need for acknowledgement from the staff about the baby's well-being. Some were anxious about taking responsibility for the preterm infant. However, when the parent was able to take responsibility for the caregiving, the clinical setting was adequate.

> "She is a preterm so she sleeps a lot. But I feel like she is safe in the midst of it all. She is not just sleeping, she is lying there snuggling. That's how I feel." (mother)

Moreover, some parents who felt abandoned in their contact with the infant also expressed a sense of being somewhat neglected by the staff. The situation for parents with a medically stable infant could be viewed by the staff as more or less normal and consequently the psychological support the staff provided could be experienced by the parents as insufficient.

> "If there had been a ward that was more in-between NICU and the post partum ward. There you would have a few rooms or a unit for these babies that might need some more help. Or for the parents with babies needing more help". (father)

In spite of the difficulties described in the parents' caregiving of infants born late preterm, the narratives from this group included fewer descriptions of traumatic experiences compared to parents of infants born early preterm. There were statements in the material about being grateful for the possibility to stay together as mother and father.

Hindering and facilitating factors attributed to the clinical practices – experiences in early and late PTB

To be separated from the newborn infant was sometimes experienced as very difficult and parents were especially subjected to stress when the baby was transferred to a different hospital or when they were in the post-partum ward without the infant. It was described as facilitating when the professionals in the NICU encouraged the parents to have faith in the future. Many descriptions of strong-willed infants were directly or indirectly presented as originating from the staff. Mothers of infants born late preterm, who experienced separations from the infant, described it as facilitating if the father or another relative was with the baby, or if she got reports about the baby's status.

Stress and circulating IL-6 in parents of preterm and term infants (IV)

In study IV, no differences were found between the two groups of mothers or fathers regarding level of education and proportions of individuals born in Sweden. All couples cohabited or were married, and one woman was single. The mean age was significantly higher in the fathers of term infants compared to those of preterm infants. Age was therefore included in the analyses of group differences in fathers. No age difference was found between the preterm and term group of mothers. All women included were first-time mothers, but four fathers in the term group and none in the preterm group had a previous child. Both women and men in the preterm group reported higher marital support (the Barnett scale) than the women and men in the term group. There were no significant differences in the mean scores of the parents' evaluation of the infants social emotional development (ASQ:SE) between the preterm and term groups at infant age four months.

When measured during the first week post partum, perceived stress scores were higher among mothers of preterm infants in comparison to mothers of full term infants but there was no difference between the two groups of fathers. At infant age four months there was no difference between the two groups of mothers or fathers. Sub-group analyses of perceived stress between parents of infants born early preterm (after 24-33 weeks) and parents of infants born late preterm (after 34-35 weeks) in comparison to parents with infants born at term showed that the mean stress level in mothers of infants born early preterm was higher at both time-points, compared to the term group (p=.035), see figure 8. Fathers of infants born early preterm reported higher stress early post partum than fathers of infants born late preterm (p=.045).

The mean IL-6 values did not differ at any time-point between the two groups of mothers and fathers, respectively. In both groups of mothers, IL-6 levels decreased significantly from 24-72h hours post partum to infant age four months (p<.001).

Perceived stress and levels of IL-6 were not significantly correlated at any time-point in either mothers or fathers (p=>.10). When mothers and fathers in preterm and term groups were analyzed separately, similar non-significant relations were observed.

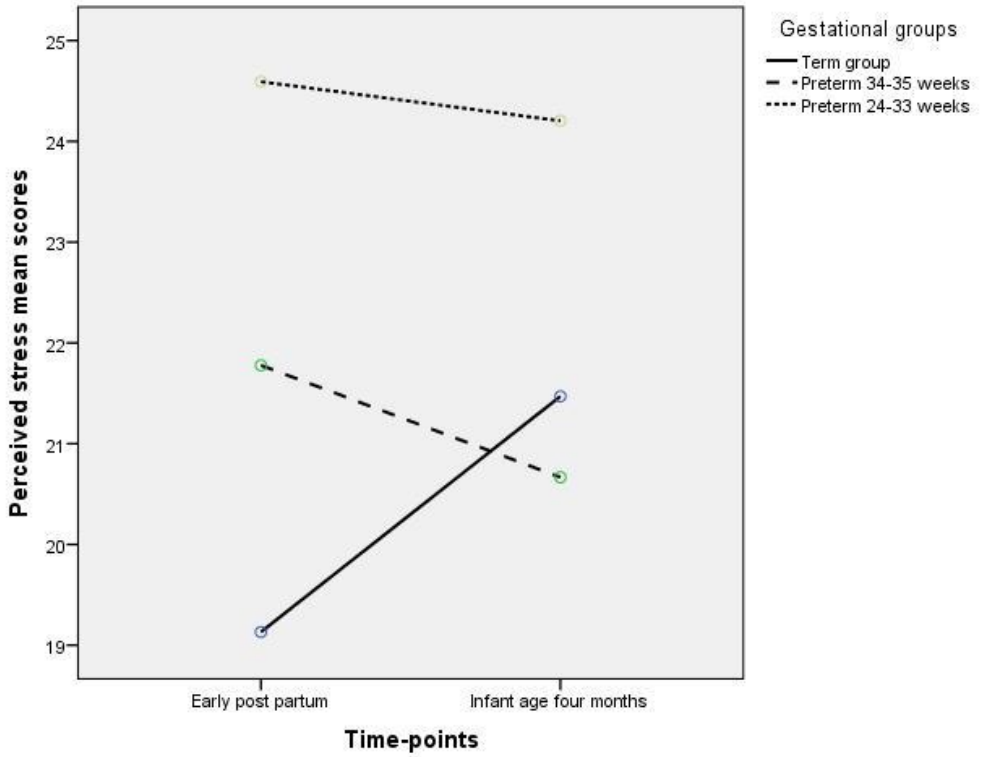

Figure 8. Mothers' mean scores on the Percived Stress Scale at early post partum and at infant age four months in the term group and preterm groups with infants 24-33 gestational (early preterm) weeks and infants 34-35 gestational weeks (late preterm). The mean stress level in mothers of infants born early preterm was higher at both time-points, compared to the term group, while the other differences were not statistically significant.

In the preterm group, twelve mothers and ten fathers scored in the upper quartile of PSS total score (25-46) at infant age four months. Twenty-six mothers and twenty-five fathers scored below the upper quartile (4-24). The logistic regression model included the variables: parent's gender, age, level of education, country of birth, PSS scores at time-point 1, marital relationship scores, evaluation of the infant development scores as well as gestational length in completed weeks. The model significantly predicted high stress scores at infant age four months (omnibus chi-square=17.944, df =8, p=.022) and 47.6% of the predictions of high stress were accurate. Only PSS scores from early post partum were significantly associated with high stress levels at infant age four months, p=.012, OR=1.09 (95% CI 1.02-1.16). The parent's evaluation of the infant's social emotional development (ASQ: SE) was close to significant in the model, p=.053. The model accounted for 32% of the variance (Nagelkerke R^2).

DISCUSSION

The overall aim of this thesis was to study PTB from different perspectives, to gain further understanding of the psychosocial contribution to PTB, of the suggested pathways for psychosocial contribution via inflammatory responses and of the consequences of PTB for parents' health and development of the caregiving.

The results show that depressive symptoms during pregnancy contribute to an increased risk of PTB (I). Moreover, we found support for the suggested inflammatory pathway for such contribution (II). These results will be addressed in the first part of the discussion. Findings also reveal hindering and facilitating factors in the development of parents' caregiving after PTB (III) as well as elevated stress levels in parents of preterm infants (IV). Moreover, it was found that high levels of stress at infant age four months in parents of preterm infants were predicted by stress levels early postpartum (IV). The results concerning parents and parenting will be focused on in the second part of the discussion, together with suggestions regarding possibilities of promoting parents' caregiving and well-being after PTB. Finally, methodological issues relating to the present work will be discussed.

Intersections of psychobiology in PTB

Findings in this thesis suggest that antenatal depressive symptoms increase the risk for preterm delivery (I) and moreover, indicate an association between antenatal depressive symptoms and enhanced inflammatory responses to PTB in mothers and neonates (II). These results, although somewhat preliminary regarding study II, derive from attempts to apply the growing knowledge of a connection between emotional factors and inflammation to the clinical challenge of PTB. This first part of the discussion will be a further attempt to appreciate the intersections of psychoneuroimmunology and PTB research.

As described in the introduction section, successful pregnancy was previously regarded as a Th2 phenomenon with a dominance of anti-inflammatory agents, but this notion has been revised and a more complex picture of cytokine balance is now recognized. In this respect, the importance of Treg cells has recently been emphasized (Mjösberg et al 2010; Sverremark-Ekström 2010). Similarly, an imbalance in the Th1/Th2 subsets has been described in psychopathology, e.g. with a shift towards a pro-inflammatory milieu in

depression (Myint et al 2005; Song et al 2009). Moreover, new research suggests important functions for Treg cells also in depression, (Miller 2010) and depression has been associated with decreased Treg cytokine activity (Dhabhar et al 2009; Myint et al 2005) and an increase in Th17 cell activity (Chen et al 2011).

In study II, negative emotions were associated with an increase in pro-inflammatory IL-6 and IL-8 activity in maternal blood. This is in accordance with findings by Christian et al (2009) showing that maternal depressive symptoms during pregnancy are associated with elevation of IL-6 levels. It is suggested that IL-6 is important in the generation of Th17 cells from naïve T cells (Kimura & Kishimoto 2010b) and accordingly, IL-6 is thought to regulate the Treg/Th17 balance through the inhibition of Treg activity (Kimura & Kishimoto 2010a). Furthermore, Treg activity is shown to inhibit IL-8 production in certain immune cells (Tiemessen et al 2007) and conversely the Th17 cytokine IL-17 could promote the production of IL-8 (Kolls & Lindén 2004; Roussel et al 2010).

It can be speculated that one mechanism of action for the link between depressive symptoms and PTB could be that depressive symptoms cause or result from an imbalance in the Treg/Th17 development. Such an imbalance has been suggested in depression (Chen et al 2011) and to have a putative role in pregnancy loss (Wang et al 2010). Moreover, Kisilewicz et al (2010) suggest that there is a diminished expression of Treg in women with preterm labor.

In study II, it was also found that maternal negative affect (NA) was associated with elevated levels of IL-6 and IL-18 in cord blood. This is in line with a study by Mattes et al (2009) where neonates exposed to maternal depressive symptoms during pregnancy showed higher production of IL-6 as well as of IL-10, compared to unexposed newborns. To speculate, negative maternal emotions could play a role in the onset of a fetal inflammatory response that in turn could contribute to the onset of delivery. Elevated levels of IL-6 have been reported in the fetal inflammatory response syndrome (FIRS) (Gotsch et al 2007) and can occur in the absence of infection (Vaisbuch et al 2011).

Not all women who report depressive symptoms or NA show elevated levels of pro-inflammatory markers and only some women who experience negative emotions deliver preterm. This might be due to individual differences in the immune-brain crosstalk that have been reported previously, reviewed by Cohen and Hamrick (2003). For example, such

differences could be due to diverse patterns in glucocorticoid binding (van Zuiden et al 2009) or in HPA axis responsivity (Capuron et al 2003). There is also data suggesting that early-life stress (and/or childhood maltreatment) act as a predisposing factor for increased inflammatory responses later in life (Carpenter et al 2010).

In study I, the proportion of women with antenatal depressive symptoms was higher among the women who delivered preterm, in line with previous findings, e.g. reviewed in Grote et al (2010), whereas in study II there were no differences in affectivity between the preterm and term groups. The findings from study II are in line with a few other studies, such as one by Andersson et al (2004). However, the time-points and methods for measurements differ between studies I and II, which might explain the contradictory findings.

In study II, maternal levels of IL-8 were lower in the preterm group than in the term group. Lower levels of IL-8 in the human myometrium in PTB compared to term labor has previously been found (Elliott et al 2000) as well as lower stimulated levels of inflammatory markers in pregnancy before 34 weeks compared to after 34 weeks, suggesting a normal increase of inflammatory responsiveness with gestational length (Brewster et al 2008).

When looking at the inter-relationship between negative emotions, elevated inflammatory markers and PTB, many questions remain regarding individual differences and also the potential importance of the timing of psychosocial exposure during pregnancy. However, given the importance of the balance between different T cell subsets, it is still not known whether the balance should be precise at a certain time-point, or if it instead is a sequential regulation of different states (van Mourik et al 2009). In theory, a to and fro loop between a pro- and anti-inflammatory milieu, might be one explanation of the difficulties in pinpointing what and when certain exposures becomes harmful. Maybe it is not only the timing of the exposure during pregnancy that is important, but also the timing of exposure in regard to the momentary Th cell subset(s) dominance.

Fetal programming

In line with the suggestions by Carpenter et al (2010) concerning early-life predispositions for increased inflammatory responsiveness, the findings in study II of higher pro-inflammatory markers in cord-blood of preterm neonates exposed to maternal negative mood, could indicate a programming effect on the fetal immune system. It has been suggested that perinatal stress can alter immune and HPA functions in the infant, reviewed

by Merlot et al (2008) and also further on in life, reviewed by Coe & Lubach (2005) and Entringer et al (2010). Based on primate studies, Coe and colleagues have suggested that the timing of stress during pregnancy might determine the kind of influence on immune function. Blood sample cultures from newborn offspring exposed to stress in early pregnancy showed enhanced immune responses, while stress in later gestation was associated with inhibited immune response (Coe & Lubach 2005; Coe et al 1999). Prenatal stress has also been associated with later psychological and psychiatric problems during childhood, such as anxiety and impulsivity and lower cognitive performance, reviewed by Glover (2011).

Supposedly, also prematurity per se could imply altered immune and endocrine responses, possibly due to immaturity in the brain as well as in the peripheral systems. Moreover, the preterm infant is often exposed to early, repeated and stressful postnatal interventions. Research in this area indicates that children born preterm have different cortisol reactivity when exposed to stress later on and they also show increased sensitivity to parental behaviors, indicating altered early programming (Brummelte et al 2010). Moreover, it is suggested that children born preterm more often develop mental health problems when they have a parent suffering from depression (Nomura et al 2007). However, there are also promising results from studies on maternal antenatal distress and infant cortisol levels, indicating that maternal sensitivity to the infant could modify effects of fetal programming (Kaplan et al 2008).

Development of parents' caregiving after PTB

The findings in study III indicate difficulties for parents in the caregiving of infants born early preterm. These difficulties could arise both from emotional circumstances such as fear or insecurity or the experience of conflicting demands, and also from physical hinders such as the infant being in an incubator. The mothers and fathers of infants born early preterm seemed to go through similar processes. The circumstances described have also been previously reported as sources of distress in parents of infants born early preterm (Arockiasamy et al 2008; Holditch-Davis & Miles 2000; Jackson et al 2003; Reid 2000).

It is suggested that the parent's caregiving system is activated when the parent perceives a situation as frightening or stressful for the child (George & Solomon 2008). With an infant born early preterm, it is plausible that some parents could be constantly on the alert from experiencing the acute needs of the infant. Some results in study III could be viewed as

illustrating the parent's agony of having the caregiving system highly activated but not being able to fulfill the goal, i.e. to give comfort to the baby. This kind of helplessness has been reported in similar studies e.g. from Hollywood & Hollywood (2011). However, the findings in study III also indicate that some parents are able to adjust and to perform caregiving, despite the physical hinders. These parents seem to attribute certain qualities to their infants that, regardless of the actual state of the child, seem to guide their hope and caregiving in a positive way. These parents act *as if* the infant will survive (which most infants will also do), *as if* their presence in the NICU is important for the infant and *as if* every minute that passes is a good sign. It can be assumed that some parents already posses this ability to cope, but there are also potential opportunities for staff and partners to support the development of such coping.

Parents with infants born late preterm also reported emotional hinders to caregiving, particularly when receiving few or weak infant cues. One can speculate that some parents with infants who are mostly asleep could be at risk of not getting enough signals to activate their caregiving system. Borghini and colleagues (2006) found that mothers of low-risk infants born preterm showed higher rates of insecure attachment representations, particularly disengaged representations of their infants, compared to mothers with high risk infants born preterm. The authors postulate that when the infant's needs are not noticeable, mothers experience withdrawal of parental emotions and difficulties in establishing a close relationship with the infant. In study III, the results also indicate that some parents with infants born late preterm could risk similar difficulties as those of parents with infants born early preterm. Namely, they risk having a highly activated caregiving system due to fear and worry about the infant not giving any signals but being without enough opportunities to perform caregiving. Furthermore, parents could experience the drowsy baby as being potentially ill and therefore judge their caregiving as insufficient. Previous research has suggested that mothers with sleepy and drowsy preterm infants are still at increased risk of elevated stress one year after birth (Veddovi et al 2004).

Stress in parents

In study IV, mothers of infants born preterm were found to be at risk of elevated stress during the early postpartum period. This is in line with previous findings, e.g. by Konstantyner et al (2007), Treyvaud et al (2010) and Younger et al (1997). However, in study IV, the elevated levels of stress in mothers during early postpartum declined over time and were comparable

to levels in the term group at infant age four months. This pattern of normalization over time has been found previously (Lau & Morse 2003; Miles et al 1992), and is promising as it indicates parental adjustment over time. Nevertheless, when specifically considering mothers with *early* PTB, these mothers are less likely to report such a decline in stress levels over time. Presumably, the family situation after early PTB could be considerably affected by the vulnerable infant in combination with parent-infant separations due to a long stay in the NICU. In a recent study, mothers of infants born very preterm reported high levels of stress during the first year after childbirth (Garel et al 2007) and post-traumatic stress has been shown subsequent to early PTB in both mothers and fathers (Kersting et al 2004; Shaw et al 2009). Thus, the parents of infants born early preterm seem to be a vulnerable group.

In study IV, no differences were found in stress levels between the preterm and term groups of fathers; however fathers of infants born early preterm reported elevated stress levels post partum compared to fathers of infants born late preterm. Although increasing numbers of fathers are involved in caregiving already from birth, there still seems to be scope for large individual differences in the development and understanding of the early fathering role (Johansson 2011; Seward et al 2002). In study III, some fathers emphasized their desire to be close to the infant, while others early on appreciated the possibility to leave the hospital. Moreover, some fathers highlighted their own desire for close proximity to the infant, while others appeared to view the caregiving primarily as a joint system together with the mother and thus seemed to be satisfied if the mother had close contact with the infant. Similar differences in fathers have been reported e.g. in a study from Canada (Arockiasamy et al 2008). In future studies as well as in clinical practice, it is important to appreciate the differences in the understanding of early fatherhood.

Furthermore, it was found in study IV that parents of preterm infants experiencing high levels of stress in the early post partum period were at risk of prolonged stress during the coming months. Effects of caregiving stress on immune function have been increasingly reported, reviewed in Kuster & Merkle (2004). However, we did not find an association between stress in parents and serum levels of pro-inflammatory IL-6. Similarly, Lau & Morse (2003) studied perceived stress and biological markers (cortisol and tribulin) in parents of preterm and term infants five times during the first 16 weeks after PTB and reported no associations. It is difficult to draw justified conclusions regarding the psychobiological health of parents after PTB from the research to date since the methodology and time-points for measurement differ between studies. However, given that perinatal stressors have been linked to negative

consequences for immune regulation in offspring (Fang et al 2011) and since the mental health status of the parent might be of particular importance when the infant is born preterm (Nomura et al 2007), the need for further studies of parents' health after PTB could be emphasized. Future studies should preferably include large samples in order to better elucidate risk and resilience of parents after PTB.

Possibilities of promoting parents' caregiving and well-being after PTB

The results from study III show that some parents of infants born late preterm experience a need for further attention when in postpartum care. Parents could benefit from acknowledgement of their situation as being different from that of parents with full term infants. Moreover, these parents could need help in interpreting their infants' needs since the infants provide few cues to guide the caregiving. Previous studies have suggested that interventions to increase parent-infant closeness are beneficial for parents' tendency to respond to the infant signals in families with healthy infants (George & Solomon 2008). The results from study III indicate that a close physical connection, such as skin-to-skin contact, could be significant for the development of the caregiving system as well as for the parent's ability to read the infant's signals after early PTB. Possibly, skin-to-skin interventions could also be beneficial for parents of drowsy infants born late preterm who are placed in regular post-partum care. Information about the frequency or the duration of skin-to-skin contact or time to first skin-to-skin contact was not included in study III. Only information about whether or not such contact had occurred and the parent's associated experience was considered. However, a positive impact of early and close parent-infant contact is suggested by an increasing number of studies. Skin-to-skin contact provided through kangaroo care (Blomqvist et al 2011; Feldman et al 2002; Roller 2005; Tessier et al 2009) and close contact when parents are able to hold their infants (Arockiasamy et al 2008; Reid 2000; Sæter Hansen 2010; Sullivan 1999), have been reported to facilitate the bonding process and to increase parental confidence in both mothers and fathers. Moreover, positive effects from skin-to-skin care on the development of infants born early/late preterm as well as term have been shown (Bergman et al 2004; Dodd 2005; Moore et al 2009). It would be valuable to evaluate skin-to-skin interventions for the potential promotion of parents' caregiving behaviors after late PTB.

In study IV, high stress levels experienced at infant age four months in parents of infants born preterm, were predicted by stress levels reported early postpartum, indicating that

vulnerable individuals could be identified early on. Transition to parenthood has been described as a potentially stressful time when the new parent's own need for support increases (Bowlby 1988). Bowlby (1969/1982) has described attachment as an essential construct across the whole lifespan, reflecting that human beings of all ages need someone to provide a secure base for them when life is experienced as stressful. Accordingly, it could be presumed that parents experiencing stress also have an activated attachment system and a need for comfort. However, a balance is necessary between such a need and the caregiving behavior. This balance could be obtained if others provide the parent with a secure base (Bowlby 1988). It was indicated in study III that the mother and the father might act as a secure base for each other. In a study of fathers experiencing PTB, most fathers reported that their partners acted as their main source of emotional support (Sloan et al 2008). Furthermore, it has been stated in previous studies of Swedish parents of preterm infants that both parents wish to facilitate the father's presence in post-partum and in neonatal care (Lindberg et al 2008; Nyqvist & Kylberg 2008). Interestingly, an unexpected result in study IV was that, within a few days after the birth, parents of infants born preterm rated their marital relationship more positively than parents of term infants. This could indicate a strengthening effect on the relationship from sharing the experience of PTB, as described by fathers of preterm infants in another Swedish study by Lindberg et al (2008). Family rooms in the antenatal and post partum wards could facilitate the parents' mutual support. Moreover, results from study III indicate that the balance between the parent's own security-seeking behavior and the caregiving behavior could be facilitated if parents are encouraged to believe in the infant's capacity as well as in their value as parents. These findings suggest important functions for the professionals in the NICU to act as bridge builders between the parent and the infant. In study III, such positive functions provided by the staff were reported. However, there might be room for improvement regarding the support of parents experiencing considerable amounts of worry and in particular of parents who refrain from attending the NICU.

Methodological considerations

There are limitations and methodological issues concerning the studies included in this thesis that should be taken into account when interpreting the results.

Study I

In the original national sample, that study I is based on, over 30% of the women eligible declined participation. Moreover there was a small number of women (n=23) who did not complete the EPDS. However, the study sample was similar in background characteristics to the whole birth cohort of Swedish women giving birth and also the proportion of women reporting depressive symptoms is similar to other studies (Gavin et al 2005).

The EPDS has been developed for the detection of depressive symptoms in the post-partum period, but it has also been validated and used for antenatal samples (Murray & Cox 1990). A recent Swedish validation study of EPDS has suggested a cut-off level of 12/13 for detection of depressive symptoms during pregnancy (Rubertsson et al 2011). However, two previous Swedish studies have used a lower cut-off level, 9/10, for antenatal samples (Josefsson et al 2001; Seimyr et al 2004). In study I, the cut-off point 11/12 was chosen in accordance with a previous Swedish validation study (Wickberg & Hwang 1996). Thus, we have shown that also moderate levels of depressive symptoms elevate the risk of PTB.

Data on some possible confounders were lacking in the material in study I and could therefore not be controlled for. For example, we could not adjust for pre-pregnancy BMI, due to a large amount of missing data regarding either height or weight. Previous studies have suggested that low BMI may be a predictor of PTB (Orr et al 2002) and it has also been proposed that low BMI in combination with depression further increases the risk of preterm labor (Dayan et al 2002). We also lacked information on previous PTB which is a known risk factor for PTB among multiparous women.

Regarding the sub-group analysis with young women, the confidence interval was fairly large (95% CI=1.37-7.19) and the result should be interpreted with appropriate caution.

Studies II and IV

Studies II and IV are quasi experimental studies, conducted in clinical settings and associated limitations need to be considered. Participants in studies II-IV were informed and asked

about participation in connection with the birth of their child. Plausible reasons for declining participation might concern fear of blood-sampling, a very negative experience of giving birth or a high degree of labor pain. However, regarding fear of blood-sampling, some participants were included and only contributed to the interview and questionnaire parts of the study. Still, one limitation of the studies is the lack of information on background variables regarding those who declined participation and women who were not approached (i.e. women who delivered when no member of the research team was present) and thus, there might be differences between the participants and the non-participants.

Regarding the participants included, there were no statistically significant differences in socio demographic background between the preterm and term groups in studies II and IV, although in study IV the fathers were significantly older in the term group. Age was adjusted for in the multivariate analyses of the fathers' variables in study IV. The preterm and term groups of women in study II differed regarding medical treatment. For example, Antibiotic infusions were given during labor to the majority of women in the preterm group, but only to a few women with term delivery. A few of these individuals could have had antibiotic infusions at additional time-points due to longer hospitalization between the rupture of fetal membranes and the actual delivery. However, most infusions were given close to the birth of the baby and the majority of the blood samples taken during labor (study II) were obtained in the early stages of the antibiotic infusion or even before infusion. Consequently the effect on labor cytokine levels was presumably small. Nevertheless, the antibiotic treatment might have influenced post partum cytokine levels (study IV). Also, the sampling among the women for bacterial cultures was not complete and therefore not adjusted for when comparing cytokine levels. In particular, there were large numbers missing in the term group, due to the fact that sampling for bacterial cultures was not part of the regular routines at the delivery ward. Furthermore, only women with early PTB were given corticosteroid treatment (betamethasone). This fact further limits the possibilities of subgroup analysis of inflammatory markers in early versus late preterm delivery, and in study II we did not include such analyses. In study IV, few exclusion criteria were applied for the fathers. However, questionnaire data showed that the proportion of men who reported physical disease, use of tobacco or medicine was small. Nevertheless, due the limited sample size in study IV, we did not adjust for such possible confounders.

Cross-sectional data were used in study II, and conclusions on causality cannot be drawn. Moreover, measurement started during delivery (study II) or early post partum (study IV).

This limits the possibilities for further understanding of the development of psychosocial health in parents after PTB.

In study II, depressive symptoms were assessed through interviews post partum with the aim to inquire about previous depressed mood during pregnancy. Retrospective measures have been criticized regarding potential recall bias, that is, participants with more negative experiences at the time of the interview could be expected to recall more depressive mood from past time periods. In study II there were no differences between preterm and term groups in the proportion of women reporting depressive symptoms. Consequently, it could be assumed that recall bias did not play a large role. Furthermore, it might be argued that assessment of self-reported emotions during the time surrounding childbirth renders difficulties when it comes to interpretation of such reports. Positive and negative affect (Study II) are thought to be fairly stable constructs (Watson & Walker 1996). Nevertheless, previous research with subjects in early transition to parenthood indicates that personality traits might differ before and after childbirth (Jonas et al 2008; Sjögren et al 2000). In the studies included in this thesis, however, all participants completed the self reports during the same period of life and could therefore be comparable.

The PSS has been validated for perinatal groups (Chaaya et al 2010). In the validation study as well as in study IV, the mean stress levels were lower in the perinatal groups than in normative samples of university students (Cohen et al 1983; Eskin & Parr 1996). Thus, there could be dimensions of stress and well-being in new parents that are not captured in general stress measurement. Future studies should further investigate appropriate measurement of stress during transition to parenthood.

In study II, multiplex technology (Bio-plex) was used in the analyses of serum cytokine levels, a method reported to be equal to ELISA (duPont et al 2005). Moreover, a benefit of the Bio-plex methodology in comparison with ELISA is that very small amounts of serum are needed to perform several analyses. This was valuable in study II, specifically regarding the cord samples where the quantities were very limited. However, the Bio-plex also showed limitations regarding sensitivity, and some of the cytokines were not used in the analyses due to a large number of undetectable values. For study IV, we chose a high-sensitivity ELISA to enable detection of very low levels. Samples in study II were collected during labor and were expected to show high cytokine levels, while samples in study IV were partly collected

months after the delivery, both from mothers and fathers, and cytokines levels were thus expected to be lower.

Study III

Interviewing as a research method is thought to be beneficial compared to empirical material from questionnaires, since it provides a richer source for the individual experience (Alvesson 1996). However, interview studies are also at risk of bias. Besides, for the participants, the interview situation is a social situation where the participant might feel obliged to make a good impression, which could result in biased information (Alvesson 1996). The problem of social desirability, however, has to be addressed in all research of subjective matters. In study III, assurances were made throughout the work with this study to promote the trustworthiness of the data. The time-points for the interviews were set in collaboration with the families to provide a relaxed atmosphere. The same author performed all the interviews, which could provide stability over time. However, the fact that the interviewing author was a woman and a clinical psychologist might have influenced the interviews. For some participants this might have made it easier to discuss their situation openly, while others might have felt less relaxed in the interview situation. It is also important to consider the fact that the interviews were carried out during the first eight days post partum and thus, reflect this limited period of time. Moreover, an adaptation process could have begun for some parents while others were facing a psychological trauma. Further, it is possible that the selection of participants, which was partly based on the richness of the narratives, was also a selection of participants with more negative experiences. Participants might be more anxious to share negative material and those who have faced traumatic events might also be more talkative during interviews (Rullkoetter et al 2009). Altogether, this does not reduce the relevance of the interviews included but the general picture of parents' experiences might be a brighter one. However, according to clinical experience, the parents in study III were not unique. Throughout the process of analysis the coding was compared with raw data to achieve credibility and discussed in the research team until consensus was reached. To enable the reader to judge the credibility of the findings, quotations were used for illustration of the data. Importantly, study III is based on first time parents in a Swedish setting and the findings could only be transferred to similar groups.

CONCLUSIONS

In the present work different aspects of PTB have been investigated. The results of this thesis support the notion of psychosocial contribution to the etiology of PTB via an inflammatory pathway, although more research is needed to elucidate the mechanisms involved. The findings also reveal hindering and facilitating factors in the development of parents' caregiving after PTB and elevated stress levels, particularly in parents of infants born early preterm. Moreover, it was found that high levels of stress at infant age four months in parents of preterm infants were predicted by stress levels early post partum, enabling early interventions for vulnerable parents. Support was not found for the suggested association between stress in parents and elevated inflammatory activity. The consequences of PTB for parents' immune function require further studies.

CLINICAL IMPLICATIONS

Presented below is a summary of the clinical implications for perinatal care derived from the findings in this thesis, mainly applicable for settings similar to the Swedish. This issue has been more thoroughly discussed previously in the discussion section.

- Since antenatal depressive symptoms, besides being problematic for the individual could also increase the risk of PTB, preventive interventions and/or treatment suitable for pregnant populations should be offered to mothers at risk.

- Psychosocial support, such as counseling, should be offered to parents with infants born early preterm and, in addition, to parents with infants born late preterm who report high stress levels early post partum.

- Families, with preterm infants who are placed in regular post-partum care, should be more closely monitored in order to identify parents in need of extra support regarding interpreting the infant's cues and/or interventions to reduce worry or anxiety.

- Family rooms should be provided in post-partum care for families with preterm infants to facilitate parents' mutual support.

- Skin-to-skin interventions, together with adequate instructions, should be offered families with infants born early as well as late preterm to promote development of parents' caregiving behavior.

FUTURE DIRECTIONS

Despite the increasing knowledge about PTB and its consequences, the complete image of the etiology and mechanisms involved remains to be an issue for the future. From my point of view after working with this thesis, I believe that future studies have to acknowledge the complex picture. For example, when investigating psychosocial risk factors for PTB, effects on immune parameters should be included, preferably with several assessments during pregnancy and during preterm delivery as well as delivery at term. Moreover, forthcoming research should consider possible overlaps in the immunological footprint of PTB and psychopathology and further investigate the intersections. One suggestion for future research is to study the putative immunological imbalance in PTB between Treg and Th17 and the possible role of psychosocial factors. It would be of importance to perform further studies on whether associations between maternal depressive symptoms and increased levels of inflammatory cytokines in umbilical cord blood at birth also indicate a programming effect on the infant's immune system, and if so, if the effect differs between preterm and term infants.

Since antenatal symptoms of depressed mood are a suggested risk factor for PTB, shown in this thesis as well as elsewhere, there is a need to identify women in need of support and also to provide support. However, such supportive or preventive interventions for pregnant women should be evaluated, including possible effects on gestational length and fetal outcome.

Regarding the possible impact of PTB on parents' stress, physical health and parenting it is warranted that future studies also include fathers, ideally with large sample sizes and a prospective design starting antenatally to better elucidate the development of health and disease in these parents. Moreover, it has been suggested that caregiving quality involves dimensions related to the difficulties that were identified in this thesis for parents of infants born early as well as late preterm. The impact of such difficulties on the parent-infant relationship later on in life should be further studied, especially in families with infants born late preterm. And finally, when considering the combined results from this thesis and previous studies, it could be presumed that skin-to-skin interventions can be beneficial for the development of caregiving in parents with infants born late preterm, however, such interventions should also be evaluated.

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